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From the Department of Pharmacognosy (Professor Finn Sandberg) Kungl Farmaceutiska institutet Stockholm Sweden, and the Department of Obstetrics and Gynæcology (Professor A Ingelman Sundberg) Sabbatsbergs sjukhus Stockholm Sweden

IN VITRO STUDIES OF THE MOTILITY OF THE HUMAN FALLOPIAN TUBE

Part II The Effects of Methylergometrine and Papaverine

BY

F SANDBERG A INGELMAN SUNDBERG AND G RYDÉN

In a previous paper (Sandberg *et al*, 1960), the effects of acetylcholine adrenaline, noradrenaline and oxytocin on the spontaneous motility of the human Fallopian tube were studied

This paper is a continuation of that investigation and comprises a study of the effects of methylergometrine and papaverine

Material and Methods

Material Fallopian tubes were obtained at laparatomies Only tubes with macroscopically normal appearances were used. Immediately after operation the tubes were immersed in Ringer solution The classification in sexual phases was based on the case history and correlated with microscopic assessment of the cyclical phase of the endometrium

Method The method was exactly the same as described in part I of this investigation (Sandberg *et al* 1960)

Drugs tested Methylergometrine was given as the product Methergin[R] Sandoz Papaverine was given as hydrochloride The quoted dose refers to the amount of salts given

Estimation of effects The estimation of effects was exactly the same as described in Part I of this investigation (Sandberg *et al*, 1960)

Results

Methylergometrine The dose used was 1—2 5 μg/ml No qualitative difference in response to the various doses was found Therefore, the results of different doses are listed together in Table I

Methylergometrine had no pronounced or characteristic action on the tube, the incidence of response being very low No difference in response between the four parts of the Fallopian tube was found

Papaverine The dose used was 5—15 μg/ml No qualitative difference in response to the various doses was found Therefore, the results of different doses are listed together in Table II and an example of response is given in Fig 1

The characteristic general effects of papaverine were decreased

Table I *The in vitro Effects of Methylergometrine Tested on the Fallopian Tube from 50 Non pregnant Patients*

Parameter		Phase		
		Proliferative	Secretory	Menopausal
Incidence of response		54/137=39 %	21/41=51 %	25/48=52 %
Change of motility pattern %		20	33	32
Tonus	increase %	35	24	16
	unchanged %	37	24	36
	decrease %	28	52	48
Frequency	increase %	32	24	8
	unchanged %	59	38	68
	decrease %	9	38	24
Amplitude	increase %	24	47	12
	unchanged %	44	24	52
	decrease %	32	29	36
Amplitude maximum	increase %	48	38	24
	unchanged %	8	15	4
	decrease %	44	47	72

Table II *The in vitro Effects of Papaverine Tested on the Fallopian Tube from 37 Non pregnant Patients*

Parameter		Phase		
		Proliferative	Secretory	Menopausal
Incidence of response		48/57=84%	62/67=93%	14/14=100%
Change of motility pattern %		35	35	21
Tonus	increase %	0	2	0
	unchanged %	37	39	29
	decrease %	63	59	71
Frequency	increase %	8	11	29
	unchanged %	32	42	57
	decrease %	60	47	14
Amplitude	increase %	2	7	0
	unchanged %	33	35	29
	decrease %	65	58	71
Amplitude maximum	increase %	2	2	0
	unchanged %	6	8	8
	decrease %	92	90	92

tonus, amplitude and amplitude maximum irrespective of the phase of the menstrual cycle The incidence of response is high There was no difference in response between the four parts of the Fallopian tube or between the proliferatory and secretory phase of the cycle Whereas the frequency of contractions was decreased in the proliferatory and secretory phases it was unchanged in the menopausal group

Discussion and Conclusions

In a previous investigation (Sandberg *et al* 1959) we have shown a weak oxytocic effect of methylergometrine on the non pregnant uterus in contrast to a pronounced effect on the pregnant organ The weak and indefinite response of the non pregnant Fallopian tube found in this investigation is therefore not surprising

In contrast to methylergometrine papaverine exerts a strong action on the Fallopian tube, the effect being spasmolytic on all segments without differences between the phases of the men-

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Methylergometrine exerts a weak and undecided effect, whereas papaverine has a strong spasmolytic action on the whole tube, irrespective of the phase of the menstrual cycle or the age of the patient

Acknowledgement

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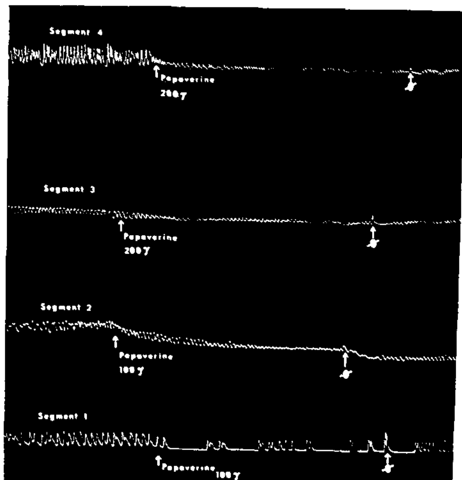


Fig 1 The effect of papaverine on the Fallopian tube from two patients in the secretory phase (Case 412 with segments 1 and 2 Case 431 with segments 3 and 4) The volume of the organ bath is 20 ml O=washing

strual cycle A corresponding effect was observed in all parts of the non pregnant as well as the pregnant uterus (Sandberg *et al*, 1961) Thus, papaverine seems to be a general spasmolytic agent for the female genital musculature

SUMMARY

The effect of methylergometrine and papaverine on the motility of the human Fallopian tube has been studied by the Magnus-Kehrer technique

metrial tuberculosis represents an advanced stage of genital tuberculosis resulting from descending intra-canalicular infection from the tubes Thus, when reporting a full term pregnancy after proved endometrial tuberculosis, he accepted only four previously published cases as fulfilling strict histological and bacteriological criteria (Halbrecht and Blinic 1960)

According to Suranyi (1962) the reported cases of pregnancy after genital tuberculosis show a clear difference depending on whether the disease was in the tubal or in the endometrial stage when drug therapy was initiated After the tubal stage of disease the vast majority were successful intra uterine pregnancies, but if the endometrial stage was reached, over 70 per cent were ectopic

In a series of 348 cases of genital tuberculosis (GT), 270 patients were married and a further 20 married during the period of observation (Ylinen, 1961) Not a single case of intra uterine pregnancy was observed in these patients, but 5 tubal pregnancies occurred All these patients had histologically (5/5) and bacteriologically (3/5) confirmed endometrial tuberculosis Not one case of intra uterine pregnancy occurred in the conservatively treated series of Ryden (1958)

The following report relates to a patient with tuberculous salpingitis (ST) and oophoritis (OT) who was seen at the Women s Clinic of Turku and who had a successful delivery after conservative surgery and drug therapy This is the first case reported in Finland

Case Report

A woman aged 23 years was admitted to the Women s Clinic of Turku University in May 1957 because of pelvic inflammatory disease of 3 weeks duration This had been preceded by intermittent dyspareunia for six months She had been married two and a half years and had been involuntarily infertile Her history was negative for tuberculosis and pelvic disorders Appendectomy had been performed six years before She had her menarche at the age of 16 years and the menstrual cycle had been regular 28–30 days

When admitted she had a sedimentation rate of 53 mm in one hour and a hæmoglobin value of 12.6 grams and the white count showed a leucocytosis of 17,300 Adnexal signs were found on bimanual examination a mass about the size of a fist on the left and slight thickening on the right In hospital

Ylinen Olli, Soiva Keijo and Castrén Olli. Acta obst. et gynec. scandinav. 4 6, 1963

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FERTILITY AFTER CONFIRMED GENITAL TUBERCULOSIS

(Report of a full term pregnancy)

BY

OLLI YLINEN, KEIJO SOIVA AND OLLI CASTRÉN

In 1956, Jedberg discussed the question of female genital tuberculosis and pregnancy and reviewed also the literature. He described two cases of pregnancy with successful deliveries and concluded that since the introduction of modern antituberculous agents the prospects for the preservation of fertility in genital tuberculosis have improved considerably. Ryden (1958) determined the incidence of pregnancy after antibiotic therapy for genital tuberculosis as reported during the years 1952–1957. Among a total of 2,118 conservatively treated cases he found reports of 20 tubal pregnancies, 12 abortions and 48 intra uterine pregnancies proceeding to term. He estimated the chances of conceiving and bearing a live child after tuberculous salpingitis to be about 5 per cent if one or both tubes are patent at the time treatment is begun. Unfortunately, both tubes are occluded in about 50–70 per cent of the cases with tuberculous salpingitis (Ryden, 1958). This percentage may be even higher, depending on the nature of the series (Ylinen and Johanson, 1955). Bilateral tubal occlusion was observed in 91.5 per cent of 142 patients examined by hysterosalpingography (Ylinen, 1961).

Halbrecht (1957) saw in healed genital tuberculosis a new ætiological factor in ectopic pregnancy. According to him endo-

metrial tuberculosis represents an advanced stage of genital tuberculosis resulting from descending intra canalicular infection from the tubes Thus, when reporting a full term pregnancy after proved endometrial tuberculosis, he accepted only four previously published cases as fulfilling strict histological and bacteriological criteria (Halbrecht and Blinic, 1960)

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When admitted she had a sedimentation rate of 53 mm in one hour and a hæmoglobin value of 12.6 grams and the white count showed a leucocytosis of 17 300 Adnexal signs were found on bimanual examination a mass about the size of a fist on the left and slight thickening on the right In hospital

she had a *continuous fever of about 38°C for four weeks* Antibiotics (tetracycline and oleandomycin) had *no effect* Examinations for tuberculosis revealed the following

Chest roentgenogram was *negative*

Urine culture (24 hours specimen) was negative for tubercle bacilli

Endometrial biopsy showed a normal proliferative endometrium The sample was negative for tuberculosis on culture and on inoculation into guinea pigs

Puncture through the cul de-sac obtained 40 ccm of serous exudate which was negative for tuberculosis on culture and in guinea pig test Bacteriological culture *revealed Staphylococcus albus* sensitive to antibiotics, *e g*, penicillin

After the investigations she received 20 grams of streptomycin combined with penicillin When the patient left the hospital after 2 fever free weeks *the left pelvic mass had decreased considerably in size and the sedimentation* rate was 40

She was *readmitted* in August, 1957, for surgery Pelvic findings were approximately the same as when she left hospital 3 months earlier The sedimentation rate was 22 and she had been free of symptoms and without fever Left salpingo-oophorectomy was performed There were slight pelvic adhesions The left ovary together with the slightly swollen tube formed an adherent mass about the size of a hen s egg The right adnexa were approximately normal and the tubal ostium was open Slight peritubal adhesions were present The left adnexa showed tuberculosis (*ST OT*) on histological *examination (Figs 1 and 2)*

Recovery was uneventful Drug therapy given was 30 grams of streptomycin and 1,000 grams of PAS

In March, 1958, bimanual examination showed no abnormality The sedimentation rate was 15 Curettage revealed a normal secretory endometrium which was negative for tubercle bacilli on bacteriological examination

The patient became pregnant about 3 years later *In September, 1960, she was in hospital because of threatened abortion at the beginning of the fourth* month of pregnancy The subsequent antenatal history was normal She was admitted to the Clinic in March, 1961, at full term She then had a slight *pre-eclamptic toxæmia and had had scanty vaginal bleeding for four days* The uterus was slightly tense but the patient had no pains Cæsarean section was performed The child was vigorous and weighed 4,000 grams The placenta had a low implantation and showed a slight degree of premature separation The right adnexa appeared normal with slight peritubal adhesions Recovery was uneventful The patient was given only 9 grams of streptomycin and was discharged on the 9th post-operative day The child was BCG vaccinated

She breast-fed her son for six months No disturbances occurred

In May, 1962, she was in the seventh month of her second pregnancy Both mother and son are well



Fig 1 Tuberculous salpingitis Numerous tubercles in tubal mucosa which shows destruction. One tubercle is seen under the serosa

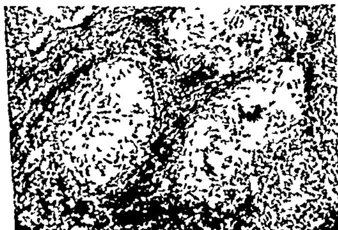


Fig 2 Tuberculous oophoritis Tubercles in ovarian stroma

Comment

A woman aged 23 years with histologically confirmed genital tuberculosis (ST, OT) was treated by conservative surgery and by moderate drug therapy with streptomycin and PAS The endometrium was free of tuberculosis She was delivered of a healthy son by Cæsarean section three and a half years later No exacerbation *occurred and she became pregnant a second time*

Discussion

The prognosis for fertility in genital tuberculosis is poor This is chiefly due to the fact that a great majority of the cases are diagnosed when tubal damage is permanent, years after the initial infection of the genitalia Ylinen (1961) concluded that "if sterility can be overcome at all in genital tuberculosis, it will be achieved through a proper long-term treatment with antituberculous *drugs in cases without severe tubal damage proved at an* early stage of the disease " Unfortunately, the possibility of early diagnosis is limited

However, in 1962 Snaith and Barns considered the prospects of pregnancy following the treatment of pelvic tuberculosis dramatically improved They reported 18 conceptions among 158 cases of pelvic tuberculosis Seven viable infants were delivered by these patients, one pregnancy was a *full-term* ectopic one One third of the conceptions were ectopic and one third ended in abortion They found an overall prospect of pregnancy in 12 per cent of patients exposed to the possibility of conception and in over 20 per cent of patients initially without gross manifestations of the disease Snaith and Barns pointed out that the prognosis as regards conception may be related to the immune response as exemplified by the degree of fibrous tissue reaction

It is apparent that succesful pregnancies after gross tuberculous changes in the tubes will remain rarities despite adequate long *term drug* therapy Many of these cases demand operative intervention with removal of the permanently damaged tubes The case presented here shows, however, that conservative surgery is justified if the tubal ostium is open and the tube shows no gross

changes at laparotomy Drug therapy and regular follow up are essential Prophylactic use of antituberculous drugs during and after the pregnancy is advisable, though in the case presented no exacerbation occurred although no such drugs were given The patient may perhaps be considered to have recovered from her genital tuberculosis

SUMMARY

The authors report a case of tuberculous salpingitis and oophoritis without endometrial involvement which was treated by conservative surgery and moderate drug therapy (streptomycin and PAS) The patient was delivered of a healthy child by Cæsarean section three and a half years after the initial diagnosis and she is now in the seventh month of her second pregnancy [1]

Despite the poor prognosis for fertility in cases with severe tubal damage, conservative surgery seems justified if the tubal ostium is open and the tube shows no gross changes at laparotomy Adequate drug therapy is essential

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[1] The patient had her second delivery by Cæsarean section on Sept. 23th 1962 The son was healthy and weighed 3950 grams No complications followed

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Soiva K and Grönroos M Acta obst et gynec scandinav 42 1 1963

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ON PERINATAL MORTALITY IN TOXÆMIAS OF LATE PREGNANCY, WITH REFERENCE TO HYPOTENSIVE DRUGS

BY

K SOIVA AND M GRÖNROOS

The maternal prognosis in toxæmia of pregnancy has improved distinctly in the last decade Doubtless many circumstances have contributed to this, such as the higher standard of living, improved antenatal care and hospital conditions, but one factor has been the management of toxæmia with hypotensive drugs This make it possible in the treatment of toxæmia to pay more attention to the infant s prognosis, a point on which the results reported are somewhat contradictory It has been said that hypotensive drugs stimulate the inadequate circulation of the uterus (Johnson and Clayton, 1955), which might improve the fœtal prognosis as was found by Beck (1959) and Anselmino (1960) in their hospital series In the latter work, however, the incidence of Cæsarean section in toxæmia had risen from the earlier percentage of 6 6 to 16 9 during hypotensive therapy Dorfler (1960) considered that active therapy, *i e* early Cæsarean section, which was performed in his series in as high a percentage of toxæmias as 53, improves the prognosis of the child According to Landesman *et al* (1957), hypotensive therapy does not influence the fœtal prognosis Reserpine administered to the mother can have a detrimental effect on the newborn, by causing congestion in the nasal mucosa (Rogers *et al*, 1957), although it does

not effect the catecholamine excretion of the newborn (Castren *et al*, 1962) The therapeutic results are influenced by many factors such as the structure of the hospital series, e g the decrease in the incidence of severe toxæmias Because of its homogeneity, a series consisting of all or nearly all the parturients of a certain district gives the most reliable picture (Kjessler, 1955, Berry and Toshach, 1960) The perinatal mortality in toxæmia in a parturient series of the city of Turku was found in a study of this type in 1958 to be only a little lower than in 1948 before hypotensive drug therapy, and improvement seemed to have been caused primarily by a decrease in neonatal mortality (Soiva and Grönroos, 1960) Hence it was considered advisable to extend the investigation to cover several years

Series

The series consisted of the deliveries in the city of Turku conducted in the Municipal Maternity Hospital of Turku in 1947–1949 and 1956–1958 (Table I) About 85 per cent of the deliveries of Turku parturients took place at the hospital in this period Four out of 5 519 parturients were lost in 1947–1949

Table I *Deliveries at the Municipal Maternity Hospital of Turku in 1947–1949 and 1956–1958*

	1947–1949	1956–1958
Deliveries	5519	4721
Maternal mortality	4	0
Number of babies born	5605	4800
Perinatal deaths	172	147

whereas there were no maternal deaths among the 4 721 parturients in the three-year period 1956–1958 It may be mentioned that the population of Turku increased in the period from about 94 000 to 118 000 but the birth rate per 1 000 inhabitants fell from 23 to 15 The therapeutic results were equally good as regards the children in both three years periods In the former period perinatal mortality (=stillbirths and neonatal deaths

during the first 7 days of life) was 3 07 per cent, in the latter 3 06 per cent

The *toxaemia patients* were selected and classified by the formula of Taylor *et al* (1954), which is suitable for studying the foetal prognosis Also included are the fairly mild forms of the disease in wich the signs may have been caused in some cases by urinary tract infection The total of toxaemia patients in the control period, 1947–1949, was 830, *i e* 15 per cent (=C series) and *during hypotensive therapy, in the years 1956–1958, 793, i e* 17 per cent (= H series) (Table II) The number of primiparae was a little greater in the C series (58 per cent) than in the H series (54 per cent) Both series included the same number of unmarried parturients Nor were there great differences of age structure between the series, though the number of parturients over 35 years of age seemed to be somewhat higher in the C series (16 compared to 12 5 per cent) As regards antenatal care, the H series received more careful care for nearly 90 per cent of the parturients were entered in the records of maternity health centres and 62 per cent had visited a centre a minimum of 6 times, of the toxaemia patients in series C 78 per cent were entered in the records of the maternity health centres and only 30 per cent had attended the centre a minimum of 6 times

The time of onset of toxaemia (Table III) was impossible to estimate in nearly half of the C series Only 64 cases could be included with certainty among the so-called chronic forms according to Taylor *et al* (1954) The comparable figure for the H series was 100 The C series had 68 per cent and the H series 53 per cent of mild toxaemias (Grade I) with blood pressure of 159/99 mmHg at the most and/or proteinuria under 0 5 G per litre Moderately severe forms (Grade II) in which the blood pressure was 160–179/100–109 mmHg and/or proteinuria 0 5–2 G per litre accounted for 20 per cent in the former and 30 per cent in the latter series The corresponding percentages for severe manifestations (Grade III) – blood pressure a minimum of 180/110 mmHg and/or proteinuria over 2 G per litre – were 12 and 17, respectively It would thus seem that the frequency of severe forms of toxaemia was greater in the H than the C series This contradicts clinical experience and is probably due to the more

Table II *Toxæmia Patients Treated at the Municipal Maternity Hospital of Turku*

	1947–1949	1956–1958
Toxæmia patients	830	793
Primiparæ	481	426
Unmarried	56	54
Age ≦ 24 years	316	325
25–34 years	380	368
≧ 35 years	134	100
Antenatal care		
No in health centre register	182	87
Insufficient data	218	61
Health centre visits ≧ 6	245	491

Table III *Time of Onset and Severity of Toxæmia*

	1947–1949	1956–1958
Before 28th week of pregnancy	64	100
In 28th week of pregnancy or later	360	542
No information	406	151
Severity		
Grade I	563	424
Grade II	169	239
Grade III	98	130
Eclampsia	21	7

careful observation of the patients during pregnancy and delivery in 1956–1958, with greater attention paid for example to elevation of blood pressure There were only 7 eclamptics in the H series, one of them post *partum* and 21 in the C series, 5 of them post *partum*

It was possible to admit only a few of the toxæmia patients (about 5 per cent) for hospital treatment before delivery *The mode of treatment in toxæmias* was conservative throughout, *i e* premature induction of labour was rarely employed Cæsarean section was necessary in 7 per cent of the C series and 4 per cent of the H series The frequency of forceps deliveries also dropped from 4 to 2 per cent. The therapy schedule for toxæmias was

magnesium sulphate, barbiturates and morphine for the C series, replaced by hypotensive drugs for the H series Oral reserpine (0 3–1 0 mg/24 hours) was used in outpatient treatment and in mild and moderately severe hospitalised cases For severe cases, reserpine was administered also by injection (1 0–5 0 mg/24 hours), and 10 per cent of these cases were given protoveratrine as well by intramuscular or intravenous injection Chloropromazine (25–50 mg) was used as a sedative when necessary Ammonium chloride was the principal diuretic employed, Parviainen *et al* (1950), chlorothiazide or its derivatives were used in some cases only during the latter half of 1958

Thus, the comparability of the C and H series is relatively good The hospital has been under the same management throughout and the main difference between the series in the therapeutic respect is only in the use of hypotensive drugs

Results

The *perinatal mortality* (Table IV) in cases of toxæmia was 4 9 per cent in 1947–1949 and 4 8 per cent in 1956–1958 Hence the fœtal prognosis had not improved during hypotensive therapy On the contrary, the stillbirth rate seemed to be greater in the H than in the C series The fœtus died before the beginning of labour in 2 2 per cent in the C and 2 7 per cent in the H series, there were 5 fœtal deaths *intra partum* in the former and 7 in the latter series The neonatal mortality appears to have been slightly lower in the H series Of the newborn in the C series that died *post partum*, 1 was a monster (hydrocephalus), and in the H series were 3 monsters (1 ancephalus and 2 with extensive umbilical hernia) The adjusted neonatal mortality was thus 2 0 per cent in the C series (=17/832) and 1 0 per cent in the H series (=8/800)

Delivery took place in the C series before the 37th week of pregnancy in 65 cases (7 8 per cent) and the perinatal mortality was 18 (28 per cent) In the H series, 74 children (9 3 per cent) were delivered before the 37th week, 20 (27 per cent) of them were lost If, on the other hand, the criterion for prematurity is the weight of the newborn, and this can be misleading especially

Table IV *Perinatal Mortality in Cases of Toxæmia*

	1947–1949	1956–1958
Number of babies born	857	832
Perinatal mortality	42 (4 9 %)	40 (4 8 %)
Stillbirths	24 (2 8 %)	29 (3 5 %)
Neonatal mortality	18 (2 2 %)	11 (1 3 %)

in cases of toxæmia, 57 babies (6 7 per cent) weighing under 2 5 kg were born in the C series, and 27 (47 per cent) of them died, in the H series there were 63 prematures (7 6 per cent) of whom 25 (40 per cent) were lost

Forty six living premature babies were born in the C series and 11 of them died Only 6 of the 44 liveborn prematures in the H series died Liveborn babies delivered before the 37th week of pregnancy also seemed to have a slightly better prognosis in the H than in the C series Total live births before the 37th week was 60 in the H series and 58 in the C series Six of the former and 10 of the latter died

The perinatal mortality in severe toxæmias was about double that in the mild forms (Table V) The fœtal prognosis did not seem to improve distinctly in severe forms of toxæmia during hypotensive therapy

There were 8 stillbirths (12 per cent) before the 37th week of pregnancy in the C series and 14 (19 per cent) in the H series The stillbirth rate during the last month of pregnancy was the same for both series (2 1 per cent)

Discussion

The perinatal mortality of toxæmia varies considerably in the series reported by different workers It was 6 9 per cent in Kaser s series (1954), 8 5 per cent in the series of Noll *et al* (1957) and only 3 75 per cent in the series reported by Vara and Timonen (1960) The mortality varies greatly, of course, with the severity of the toxæmia It was 15 9 per cent in severe pre-eclampsia and 14 7 per cent in eclampsia in Dörfler s series

Table V *Perinatal Mortality in Different Toxæmia Groups*

	1947–1949	1956–1958
Grade I cases	563	424
Perinatal deaths	21 (3 7%)	19 (4 5%)
Grade II cases	169	239
Perinatal deaths	11 (6 9%)	10 (4 2%)
Grade III cases	98	130
Perinatal deaths	10 (10 0%)	11 (8 5%)

(1960) Perinatal mortality was 4 8 per cent in mild forms of true toxæmias in Taylor's (1955) investigation In general, the perinatal mortality remains high in toxæmias and special attention must therefore be paid to the prognosis (Held, 1961, Hochuli, 1961), particularly as no disturbances have been encountered in the subsequent development of surviving toxæmia babies (Vara and Hallman, 1954) The most important reasons for fœtal loss are placental insufficiency and premature separation of the placenta (Fitzgerald and Clift, 1958)

The present study seems to confirm the view (Landesmann et al, 1957, Dorfler, 1960) that hypotensive therapy as such does not improve the fœtal prognosis in toxæmia For instance, the risk of intrauterine death of the fœtus was fairly high during hypotensive therapy, (even greater than in the control series), in deliveries before the last month of pregnancy Comparison of these two conservatively managed series – the Cæsarean incidence was fairly low in both of them (7 and 4 per cent) and premature induction of labour was generally not undertaken in either – shows that the frequency of prematurity is roughly the same (c 7 per cent) and that pregnancy terminated in both with almost equal frequency (in 8 and 9 per cent) before the last month of pregnancy Hypotensive therapy did not seem, thus, to have improved the intrauterine chances of life of the fœtus On the other hand, it seemed as if the prognosis of liveborn babies delivered during the period of investigation, especially that of prematures, did improve, perhaps thanks to better pædiatric care

It has been suggested that during hypotensive therapy pregnancy could be allowed to continue nearer term without risk (Beck

1959) Although this is doubtless true of the mother, from the point of view of improving the fœtal prognosis in severe toxæmias it is necessary to weigh the "correct moment" for the premature induction of labour (Wimhöfer and Pfau, 1955) Taylor's (1955) studies based on 4,547 toxæmias from 1931–1950, offer good guidance in this respect But new statistical investigations carried out during the period of hypotensive therapy are necessary to aid evaluation of fœtal prognosis in different forms of toxæmia at different stages of pregnancy

SUMMARY

The cases of toxæmia among Turku parturients treated at the Municipal Maternity Hospital of Turku in 1947–1949 (=C series) and 1956–1958 (=H series) were studied The number of cases was 830 and 793, respectively The incidence of toxæmia remained the same during the investigation periods (c 16 per cent) The toxæmia series were fairly well comparable in composition Severe toxæmias with blood pressure of at least 180/110 mmHg and/or proteinuria of 2 ‰ totalled 12 per cent in the C and 17 per cent in the H series but eclampsia before delivery occurred in the former series in 16 and in the latter in 6 patients The treatment of toxæmia was on the whole conservative in both series, but in the C series therapy consisted of sedatives and magnesium sulphate and in the H series of hypotensive drugs, mostly reserpine

The perinatal mortality was 4 9 per cent in the C series and 4 8 per cent in the H series The frequency of stillborn babies appeared to be slightly higher in the H than in the C series (3 5 and 2 8 per cent), especially when delivery occurred before the last month of pregnancy (19 and 12 per cent) On the other hand, the neonatal mortality appeared to be slightly smaller in the H (1 3 per cent) than in the C series (2 2 per cent) especially for premature babies of which there were equally many in both series

As the intrauterine prognosis of the fœtus in toxæmia has not improved in the course of hypotensive therapy, but the chances of survival of the liveborn baby have increased, premature induction of delivery must still be considered in some cases of toxæmia

Table V *Perinatal Mortality in Different Toxæmia Groups*

	1947–1949	1956–1958
Grade I cases	563	424
Perinatal deaths	21 (3 7 %)	19 (4 5 %)
Grade II cases	169	239
Perinatal deaths	11 (6 9 %)	10 (4 2 %)
Grade III cases	98	130
Perinatal deaths	10 (10 0 %)	11 (8 5 %)

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From the First and Second Departments of Obstetrics and Gynæcology (Professor A Tuurunen and Professor P Vara) Helsinki, Finland

PROLAPSE OF THE UMBILICAL CORD

BY

OLOF WIDHOLM* AND USKO NIEMINEN

In 1961, Cushner produced an extensive and thorough report on complications of delivery resulting from prolapse of the umbilical cord He wrote on the incidence, ætiology, and methods of treatment of cord prolapse, and on the prognosis for the babies His report also contained a detailed survey of earlier reports on the same subject, his summaries of the results of previous studies over nearly 30 years are given, supplemented, in Table I

The table reveals that the incidence of prolapse of the umbilical cord varies considerably from one series to another The average incidence in 1,116,357 deliveries was 0 39 per cent. Perinatal mortality also shows remarkable differences from series to series, but the death rate of children born in deliveries complicated by umbilical cord prolapse shows a steady and distinct fall during the period

Cushner s own series was compiled from one hospital over 61 years (Johns Hopkins Hospital, USA) During this period prolapse of the umbilical cord occurred in 424 of the hospital s 87 963 deliveries The incidence was thus 0 48 per cent The perinatal death rate in deliveries complicated by cord prolapse has fallen perceptibly in this hospital during the period under review It was at its highest in 1920–29 *viz* 69 6 per cent, and lowest in 1951–56 34 6 per cent.

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Table I *The Table Compiled by Cushner from World Literature, Supplemented*

Year	Author	Deliveries	Cord Prolapses	Incidence per Cent	Corrected Perinatal Death Rate
1927	*Sirala*	*34,098*	*125*	*0 39 %*	*40 3 %*
1932	Kurzrock	16,942	100	0 59 %	43 9 %
1940	Mengert and Longwell	9,546	58	0 61 %	46 6 %
1941	Bourgeois	36,733	155	0 42 %	40 6 %
1946	Gusberg	16,904	71	0 42 %	32 0 %
1947	Doerr	25,461	25	0 09 %	40 0 %
1948	Morgan	10,000	50	0 50 %	40 0 %
1951	Cope	59,314	350	0 59 %	27 9 %
1951	Brandeberry and Kistner	24,533	116	0 47 %	21 5 %
1951	Fenton and D Esopo	60,788	216	0 35 %	28 9 %
1951	*Cox*	*26,739*	*145*	*0 54 %*	–
1953	Jalkanen and Niemineva	58 597	244	0 42 %	19 0 %
1953	Kush	52,743	105	0 20 %	49 0 %
1953	Nelson and Arnot	9,813	22	0 22 %	9 0 %
1954	*Hess*	*16,588*	*110*	*0 63 %*	*24 9 %*
1955	Schultz	28,494	85	0 30 %	24 6 %
1956	Slate and Randall	15,578	63	0 40 %	42 8 %
1956	du Toit	59,270	406	0 80 %	32 0 %
1956	Rhodes	15,370	83	0 54 %	52 0 %
1956	*Heinsch*	*104,216*	*504*	*0 48 %*	*21 7 %*
1957	Dilworth and Ward	19 893	66	0 30 %	16 7 %
1957	Niemineva and Salovaara	39,166	102	0 26 %	21 0 %
1957	Sotto and Villeneuve	38,076	97	0 25 %	19 0 %
1958	*Ahlgren*	*84,288*	*151*	*0 18 %*	*22 2 %*
1958	Biskind	14 695	26	0 18 %	–
1959	Cushner	87 963	424	0 48 %	41 7 %
1962	Mac Laverty and Scioscia	25,542	110	0 43 %	12 5 %
1962	*Price*	*50 304*	*76*	*0 15 %*	*33 0 %*
1962	Widholm and Nieminen	74 703	309	0 41 %	10 4 %
	Total	1 116,357	4 394	0 39 %	

Death rate uncorrected

Cushner lists the following as being the most important ætiological factors in prolapse of the umbilical cord abnormal presentation, narrow pelvis, unengaged presenting part after rup-

ture of the membranes, premature delivery and multiple pregnancy The child s prognosis is worsened, according to Cushner, by the following factors late diagnosis of umbilical cord prolapse, delay in parturition after the diagnosis and premature delivery

Cushner adds that Cæsarean section has become an increasingly common method of treatment in deliveries complicated by umbilical cord prolapse, replacing the internal versions and extractions previously employed

As far as is known, Sirala (1927) was the first in Finland to publish an investigation into prolapse of the umbilical cord He compiled a series of 34 098 deliveries at the Women s Clinic of the University of Helsinki in 1912–27 which included 125 cases of cord prolapse (incidence, 0 39 per cent), with a perinatal mortality of 40 3 per cent.

Another series from the Women s Clinic of the University of Helsinki was presented by Jalkanen and Niemineva (1953) It covered two different periods, 1931–39 and 1940–45, and consisted of 58,597 deliveries in which the child s weight at birth was not less than 1,500 g The incidence of umbilical cord prolapse was 0 42 per cent, and perinatal mortality 27 9 per cent (corrected, 19 per cent) Jalkanen and Niemineva emphasized that cord prolapse occurred en 4–5 per cent of the deliveries with breech, transverse or oblique presentation As treatment, they recommend that the parturient be quickly placed in Trendelenburg s position and a Cæsarean section performed

The most recent material published in Finland is that presented by Niemineva and Salovaara (1957) It comprises 39 166 deliveries treated at Tampere Municipal Maternity Hospital in 1941–55 The incidence of umbilical cord prolapse in this series was 0 26 per cent and perinatal mortality 29 5 per cent (corrected 21 per cent) The series included only cases in which the child s weight at birth was not less than 1 500 g

Present series

Remarkable developments have occurred in recent years in treatment of parturients and of the newborn Their effect on perinatal mortality in all deliveries has been favourable, and it

therefore seemed useful to investigate in greater detail deliveries complicated by umbilical cord prolapse, particularly since the most recent published material from the First and Second Women's Clinics of Helsinki University Central Hospital (formerly, Women's Clinic, University of Helsinki) dates from a period more than 15 years ago

The present study was carried out with the special object of comparing the results with those of previous investigations No attempt has been made to throw light on the ætiology of prolapse of the umbilical cord since this has been clarified by earlier reports

The series covers 74,703 deliveries in 1951–60, in which the child's weight at birth was not less than 600 g There was a total of 309 umbilical cord prolapses, an incidence of 0 41 per cent Table II shows the annual incidence of umbilical cord prolapses

Table II *Annual Totals of Cord Prolapses, and Annual Infant Mortality*

Year	Total Cord Prolapses	Infants Dead before Admission	Deliveries with Cord Prolapse in Hospital	Perinatal Deaths in Hospital
1951	28	0	28	5 (17 8 %)
1952	22	1	21	4 (19 0 %)
1953	38	2	36	4 (11 1 %)
1954	28	1	27	4 (14 8 %)
1955	39	3	36	6 (16 7 %)
1956	38	1	37	4 (10 8 %)
1957	24	1	23	1 (4 3 %)
1958	25	2	23	4 (17 4 %)
1959	41	0	41	7 (17 1 %)
1960	26	0	26	1 (3 8 %)
Total	309	11	298	40 (13 4 %)

The incidence of prolapses by weight group was

	Number	Deaths
Maturity (weight 2,500 g or more)	234 (75 7 %)	22 (9 4 %)
Prematurity (weight 1,500–2,499 g)	65 (21 1 %)	22 (33 8 %)
Immaturity (weight 600–1 499 g)	10 (3 2 %)	7 (70 0 %)
Total	309	51

In 11 cases the prolapse of the umbilical cord and the death of the infant had occurred prior to admission to the hospital, and the corrected incidence was therefore 0 40 per cent. Table II shows the distribution of these cases by the year The table also gives the corrected death rate for infants by year, and the death rate in the total series Perinatal mortality was 13 4 per cent (40 cases) If immature births are excluded the death rate was only 10 4 per cent.

Ninety-one (29 5 per cent) of the prolapses were in primigravidæ and 218 (70 5 per cent) in multigravidæ

Prolapses occurred in 39 twin pregnancies (with 18 first twins and 21 second twins and in one triplet pregnancy the first child) The percentage of plural pregnancies in cord prolapses was 12 9 per cent.

In 150 deliveries the cord prolapsed when the cervix was fully dilated, in 141 cases when the dilatation was 5–9 cm and in 18 cases when the dilatation was not more than 5 cm

Table III *Time of Death of Infants in Relation to Birth*

Infants Died	Mature	Premature	Immature	Total	
Ante partum	13	7	2	22	84 4%
Intra partum	4	12	5	21	
Post partum	4	4	–	8	
Total	21	23	7	51 (16 5%)	
Prior to admission	5	5	1	11	
After admission	16	18	6	40	

Table III shows the distribution of the time of death of the infants in relation to birth The table also classifies the dead infants by maturity and reveals the uncorrected death rate as 16 5 per cent (51 cases)

Table IV illustrates the relationship of the prognosis for the child to the lapse of time between diagnosis and parturition The majority (86 9 per cent) of deliveries occurred within 30 minutes of the diagnosis being made In this group the death rate was 13 1 per cent, while for deliveries occurring more than 30 minutes after the diagnosis was made the death rate of infants was 20 5

Table IV *Death Rate of Infants Compared with Lapse of Time between Diagnosis and Birth (Cord Prolapse in Hospital)*

Lapse of Time between Diagnosis and Birth	Deliveries		Infant Mortality: Mature	Premature	Immature	Total	
Less than 5 min	153	259 (86.9 %)	6	8	4	18	34 (13.1 %)
5–10 "	31		3	2	–	5	
10–30 "	75		4	5	2	11	
30–60 "	24	39 (13.1 %)	2	2	–	4	6 (20.5 %)
over 60 "	15		1	1	–	2	
Total	298		16	18	6	40	

per cent. Table IV, like the subsequent tables, only lists the cases in which both cord prolapse and parturition occurred in the hospital.

Discussion

The present series is among the biggest reported in the literature, only Heinisch (1956), Ahlgren (1958) and Cushner (1959) have described larger. The material, moreover, derives from a relatively short period of time (10 years), and the results which it provides therefore reflect fairly accurately the therapeutic results of recent years.

A review of the results shows that the number of cord prolapses does not differ appreciably from the average incidence calculated on the basis of series taken from world literature (Table I).

Perinatal mortality, on the other hand, has fallen considerably compared with that in the material collected by Jalkanen and Niemineva (1953) at the same hospital. The corrected perinatal mortality rate for their series was 19.9 per cent (excluding immature births). The figure for the present series is 10.4 per cent. A comparison with the other mortality rates in Table I shows that this figure is extremely low, a lower perinatal mortality (9.0 per cent) is only quoted for the small series reported on by Nelson and Arnot (1953).

Premature births accounted for a considerable percentage (23.3) of the deliveries complicated by cord prolapse, while the

perinatal mortality in such births is very high 33 8 per cent of the prematurely born infants died, for immature births, the death rate was 70 0 per cent

The number of multigravidæ among cases of cord prolapse is remarkable 70 5 per cent of the 309 parturients were multigravidæ Cord prolapse is also frequent in multiple pregnancies 12 9 per cent of cord prolapses in the present series occurred in multiple pregnancies, compared with an overall incidence of multiple pregnancies of about five times less

Prolapse of the umbilical cord, as is understandable, represents an immediate danger to the fœtus This is supported by the fact that 84 4 per cent of the dead infants had already died before the start of labour or died in the course of delivery The death rate is increased by any delay in parturition If birth occurs within less than 30 minutes, the death rate, on the basis of the present series, is 13 1 per cent if more time elapses the death rate rises to 20 5 per cent. In many cases where the umbilical cord is compressed, death may occur in a matter of minutes Nevertheless, the correct choice of the mode of delivery is also of great importance for a successful result

The most frequently employed method of delivery in the present series was extraction of the fœtus vaginally and, where required an accompanying internal version The results achieved by this method are not so poor if the 2 immature births are excluded from the 16 dead infants This gives a death rate of only 11 8 per cent while in the cases for which the generally recommended Cæsarean section has been employed, perinatal mortality is 27 3 per cent. In suction cup deliveries there were no deaths, but these deliveries are few compared with those in other groups In most cases the selection of the method of delivery is dictated by the existing situation If for example the uterine cervix is only slightly dilated, a Cæsarean section is the only possible choice If the cervix is fully dilated and labour well advanced Cæsarean section is usually unnecessary No one method can therefore be recommended as universally correct.

Abnormal presentations of the fœtus account for a relatively large proportion of the deliveries complicated by cord prolapse

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Abnormal presentations of the fœtus account for a relatively large proportion of the deliveries complicated by cord prolapse

(62 8 per cent) About 3 5 per cent of all deliveries in the series had abnormal presentations

Table V *Death Rate of Infants, by Presentation (Cord Prolapse in Hospital)*

Presentation	Deliveries	Perinatal Mortality			
		Mature	Premature	Immature	Total
Cephalic	*111 (37 2 %)*	*8*	*7*	–	*15 (13 5 %)*
Breech	166 (55 7 %)	6	8	6	20 (12 0 %)
Oblique and transverse	21 (7 1 %)	2	3	–	5 (23 8 %)
Total	298	16	18	6	40

Table V shows the classification by presentation of deliveries complicated by cord prolapse The table also shows the distribution *of perinatal mortality by type of presentation*

Table VI *Number of Parturitions by the Different Methods, and Death Rates of Infants (Cord Prolapse in Hospital)*

Method of Delivery	No. of Births	Perinatal Mortality			
		Mature	Premature	Immature	Total
Extraction	121 (40 7 %)	6	8	2	16 (13 2 %)
Cæsarean section	61 (20 6 %)	3	3	–	6 (9 8 %)
Spontaneous birth	56 (18 6 %)	3	5	1	9 (16 1 %)
Breech delivery	43 (14 5 %)	1	2	3	6 (13 9 %)
Forceps	11 (3 8 %)	3	–	–	3 (27 3 %)
Suction cup	6 (1 8 %)	–	–	–	– (0 %)
Total	298	16	18	6	40

Table VI shows how the deliveries were conducted after the umbilical cord prolapsed The table also illustrates the distribution of infant mortality by the method of delivery

SUMMARY

The authors describe a series of 74,703 deliveries, including 309 cases of umbilical cord prolapse The incidence of cord prolapses in this series was 0 41 per cent and the corrected perinatal mortality was 10 6 per cent

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BACTERIURIA IN PARTURIENTS AFTER *CATHETERIZATION*

BY

SIMO VIRTANEN

The occurrence of urinary tract infection after catheterization is not a new phenomenon As early as 1871 Olshausen described four parturients who developed urinary tract infections after catheterization in the puerperium The risk of infection due to catheterization is usually estimated at some 2–4 per cent (Jackson and Grieble, 1957, Kass 1957, 1960b, Clarke and Joress, 1960), though series have been published in which the incidence of infection is much higher *e g* Marple (1941) 8 7 per cent, Davis *et al* (1959) 29 per cent, and Kaitz and Williams (1960) 31 7 per cent

The risk attendant on catheterization is particularly high for persons liable to urinary tract infections, *e g* patients with urinary tract anomalies or obstructions, with disorders of the nervous system associated with disturbance of bladder function, and diabetics (Jackson and Grieble, 1957, Beeson, 1958, Prather and Sears, 1960) With some slight exaggeration, Roberts (1959) stated that the risk of catheterization for diabetics approximates to that of thyroidectomy

The post-partum atonic, sometimes damaged, insensitive bladder, with residual urine, favours the development of infection during the puerperium (Ball, 1951, Eastman, 1956, Zinser, 1955) For this reason catheterization of parturients might be

expected to predispose to iatrogenic infection. To verify the risk of infection which catheterization involves for the parturient, the following investigation was undertaken, using a quantitative bacteriological method.

Material and techniques

The series comprised 204 parturients from Turku Municipal Maternity Hospital, 93 of them (45.6 per cent) were primiparæ and 111 (54.4 per cent) multiparæ. Their mean age was 25.4 ± 0.4 years, and they had consulted the Maternity Welfare Centre in the normal way during pregnancy. The bacterial count of a catheter specimen of urine taken on admission in each case was negative or contained less than 10,000 organisms/ml. All deliveries were normal, with head presentations, and all parturients were catheterized only on admission and on discharge. None of them received chemotherapeutic drug treatment while they were in hospital.

On admission to hospital, after the external genitals and perineum had been washed with soap and water and the pubic hair shaved the area of the urethral meatus was cleansed with 0.1 % Bradosol (Ciba) solution. A rubber Nelaton catheter was employed, and catheterization was performed in the delivery room with good visibility and by ordinary staff. On discharge, usually on the seventh day post partum, catheterization was performed in the ward using a metal catheter. The sterility of the catheters was checked from time to time. No contamination was found on any occasion.

The treatment of the specimens, the study of the urinary deposit, bacterial identification, sensitivity tests and count were performed as described earlier (Virtanen and Kasanen 1962). A count of over 10 000 bacteria per millilitre was taken as indicating true bacteriuria (Boshell and Sanford 1958, Merrit and Sanford 1958. Davis *et al.* 1959).

The urine sugar and albumen and hæmoglobin of all the parturients were tested routinely, and their blood pressure was measured.

Results

The results of the bacterial counts are given in Table I True bacteriuria (> 10,000 organisms/ml) was found on discharge in 17 parturients (8 35 ± 2 0 per cent) The bacterial strains isolated are listed in Table II Sensitivity determinations were

Table I Bacterial Counts on the Catheterized Urine Specimens of 204 Parturients

	Organisms ml							
	0	10^1-10^3	10^3-10^4	10^4-10^5	10^5-10^6	10^6-10^7	$>10^7$	Total
On admission	177	18	9	0	0	0	0	204
On discharge	168	14	5	7	1	1	8	204

Table II *The Bacterial Strains Isolated*

Strain	Organisms/ml			
	On Admission		On Discharge	
	$\leq 10^4$	$>10^4$	$\leq 10^4$	$>10^4$
Escherichia coli	4	–	12	7
Citrobacter	–	–	–	1
Klebsiella	1	–	1	–
Achromobacter	–	–	1	1
Proteus mirabilis	1	–	1	1
Staphylococcus epidermidis	11	–	4	6
Streptococcus α hæmolyticus	3	–	–	–
Streptococcus non hæmolyticus	–	–	–	1
Candida	7	–	–	–
Total	27	–	19	17

made as described previously to sulphadiazine, penicillin, tetracycline, chloramphenicol, nitrofurantoin, and methenamide mandelate Disregarding the resistance of gram negative rods to penicillin, 11 of the 17 strains isolated from cases of true bacteriuria were sensitive to all the drugs, 3 were resistant to one and 3 resistant to 3 drugs No completely resistant strain was detected

In only one case were leucocytes found in the urinary sediment. The patients were symptom free and afebrile.

Discussion

In a previous investigation at the same maternity hospital and on a series of comparable composition the present writer (Virtanen, 1963) found an incidence of 2.45 ± 1.1 per cent of bacteriuria developing after parturition and during the puerperium. The difference between this and the incidence of 8.35 per cent for the present series is statistically significant ($0.001 < P < 0.01$). The risk of infection associated with catheterization of normal parturients can be assessed at 5–6 per cent.

Brumfitt *et al.* (1961) found that 4.7 per cent of uncatheterized, and 9.1 per cent of catheterized, normal parturients developed puerperal urinary infection. The difference, in this material, was not statistically significant. On the other hand, parturients catheterized because of complicated delivery showed a significantly higher incidence of urinary infection, 22.8 per cent. A particularly high percentage of infection, 40.6, was noted by the authors in parturients who had to be catheterized to relieve retention of urine.

The bacterial strains isolated from cases of bacteriuria represented 6 different species, and two thirds of these isolated strains were fully sensitive to chemotherapeutic drugs. A coagulase and mannitol negative Staphylococcus epidermidis (Bergey 1957) part of the normal mucosal flora, was found in 6 cases. All this suggests that nosocomial cross infection was rarely involved but that bacteriuria developed from the bacteria normally present in the lower urethra and carried to the bladder during catheterization. Although not all patients with bacteria in the bladder develop pyelonephritis, each patient with bladder bacilluria must be regarded as susceptible to pyelonephritis (Editorial, 1960; Kass, 1960c). For this reason unnecessary catheterization of parturients should be avoided. Catheterization is not usually necessary for a bacteriological diagnosis since quantitatively tested, mid-stream voided specimens

Results

The results of the bacterial counts are given in Table I True bacteriuria ($> 10{,}000$ organisms/ml) was found on discharge in 17 parturients ($8\ 35 \pm 2\ 0$ per cent) The bacterial strains isolated are listed in Table II Sensitivity determinations were

Table I *Bacterial Counts on the Catheterized Urine Specimens of 204 Parturients*

	Organisms ml							
	0	10^2-10^3	10^3-10^4	10^4-10^5	10^5-10^6	10^6-10^7	$>10^7$	Total
On admission	177	18	9	0	0	0	0	204
On discharge	168	14	5	7	1	1	8	204

Table II *The Bacterial Strains Isolated*

Strain	Organisms, ml.			
	On Admission		On Discharge	
	$\leq 10^4$	$> 10^4$	$\leq 10^4$	$> 10^4$
Escherichia coli	4	–	12	7
Citrobacter	–	–	–	1
Klebsiella	1	–	1	–
Achromobacter	–	–	1	1
Proteus mirabilis	1	–	1	1
Staphylococcus epidermidis	11	–	4	6
Streptococcus α hæmolyticus	3	–	–	–
Streptococcus non hæmolyticus	–	–	–	1
Candida	7	–	–	–
Total	27	–	19	17

made as described previously to sulphadiazine, penicillin, tetracycline, chloramphenicol, nitrofurantoin, and methenamide mandelate Disregarding the resistance of gram-negative rods to penicillin, 11 of the 17 strains isolated from cases of true bacteriuria were sensitive to all the drugs, 3 were resistant to one and 3 resistant to 3 drugs No completely resistant strain was detected

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are adequate for the purpose (Jackson *et al*, 1958, Kass, 1960a, Turner, 1961, Virtanen, 1962)

SUMMARY

Puerperal urinary infection resulting from catheterization was investigated in 204 normal parturients by a quantitative bacteriological method A single catheterization prior to parturition produced urinary infection in some 5–6 per cent of the parturients

Catheterization of parturients for bacteriological diagnosis should be avoided, and the bacteriological study of urine should be carried out by the quantitative method on a mid-stream voided urine specimen

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1950, Kasanen *et al*, 1961) In Jäämeri s (1943) series of parturients, 75 per cent of the patients with urinary infections had no subjective symptoms Kass (1960 c) found that about 6 per cent of a series of 2,000 pregnant women had, on their first prenatal visit asymptomatic bacteriuria The present author (1962 a) diagnosed asymptomatic bacteriuria in 5 3 per cent of pregnant women at term It is obvious that the true incidence of urinary infection which develops in the puerperium can only be assessed by methodical bacteriological examination of the parturients prior to delivery and during the puerperium

This has usually been done by examining a catheter specimen of urine before and after delivery Catheterization, however, involves a risk of infection, usually estimated at 2–4 per cent (Jackson and Grieble, 1957, Kass, 1957, Kass, 1960 c), though higher figures have also been quoted, *e g* by Marple (1941) 8 7 per cent and by Davis *et al* (1957) 29 per cent The risk of iatrogenic infection, however, can be eliminated by taking a quantitative bacterial count from a mid stream voided specimen Over 100,000 bact/ml (Jackson *et al* 1958, Kass, 1960 a) have been considered an indication of true bacteriuria According to Kass (1960 c), the confidence limit of a single bacterial count is about 80 per cent for mid-stream voided specimens In the present writer s series of parturients, the confidence limit of one count was 90 per cent (Virtanen, 1962b)

To discover the incidence of true urinary infection developing during the puerperium, a bacterial count of mid stream voided urine specimens was taken for all parturients on their admission to the maternity hospital, prior to delivery, and another on a catheter specimen of urine prior to discharge from the maternity hospital

Series and Method

A mid stream voided urine specimen was taken from 250 unselected consecutive pregnant women on admission to Turku Municipal Maternity Hospital A catheter specimen of urine was taken prior to the parturients discharge from the hospital If the mid stream voided specimen showed over 100 000 organisms per

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URINARY INFECTION IN THE PUERPERIUM

BY

SIMO VIRTANEN

The incidence of urinary infections during pregnancy ranges from 0.5 to 16 per cent (Everett, 1947, Klempner *et al*, 1960), though most authors give the frequency as from 1 to 2.5 per cent (Klempner *et al*, 1960) Information on the distribution of cases of pyelonephritis between pregnancy and the puerperium is contradictory According to Nesbitt and Young (1957) and Eastman (1956), the frequency is about the same for both periods, according to Stoeckel (1938), pyelitis is the commonest complication of pregnancy while true puerperal pyelitis is rare According to Donald (1955), on the other hand, pyelitis is much more common in the puerperium than in pregnancy Of the cases of pyelonephritis during pregnancy reported by McLane (1939), 37 per cent were *post partum*, Klempner *et al* (1960) report a percentage of 26.5 In Baird's (1936 b) series, urinary infection was diagnosed in 24.5 per cent of patients on admission to a maternity hospital, while after spontaneous delivery urinary infection developed in 15.9 per cent of the cases in the puerperium

A urinary tract infection is, both generally (Saphir and Taylor, 1952) and during pregnancy (Baird, 1936 b, Mitchell and Benson, 1957) very often subjectively symptom free In more than 50 per cent of the women in a medical ward pyelonephritis was subjectively symptom-free (Halonen and Halonen,

1950, Kasanen *et al*, 1961) In Jäämeris (1943) series of parturients, 75 per cent of the patients with urinary infections had no subjective symptoms Kass (1960 c) found that about 6 per cent of a series of 2,000 pregnant women had, on their first prenatal visit asymptomatic bacteriuria The present author (1962 a) diagnosed asymptomatic bacteriuria in 5 3 per cent of pregnant women at term It is obvious that the true incidence of urinary infection which develops in the puerperium can only be assessed by methodical bacteriological examination of the parturients prior to delivery and during the puerperium

This has usually been done by examining a catheter specimen of urine before and after delivery Catheterization, however, involves a risk of infection, usually estimated at 2–4 per cent (Jackson and Grieble, 1957, Kass, 1957, Kass, 1960 c), though higher figures have also been quoted, *e g* by Marple (1941) 8 7 per cent and by Davis *et al* (1957) 29 per cent. The risk of iatrogenic infection, however, can be eliminated by taking a quantitative bacterial count from a mid stream voided specimen Over 100 000 bact/ml (Jackson *et al* 1958, Kass, 1960 a) have been considered an indication of true bacteriuria According to Kass (1960 c), the confidence limit of a single bacterial count is about 80 per cent for mid stream voided specimens In the present writer s series of parturients, the confidence limit of one count was 90 per cent (Virtanen 1962b)

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URINARY INFECTION IN THE PUERPERIUM

BY

SIMO VIRTANEN

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A urinary tract infection is, both generally (Saphir and Taylor, 1952) and during pregnancy (Baird, 1936 b Mitchell and Benson, 1957) very often subjectively symptom free In more than 50 per cent of the women in a medical ward pyelonephritis was subjectively symptom free (Halonen and Halonen,

The blood pressure of all parturients was measured, and their hæmoglobin and urine sugar and albumin were subjected to routine tests

Results

The results of the bacterial counts are shown in Table I Fully negative cultures numbered 179 (87 7 per cent) The bacterial strains isolated are listed in Table II There were 5 cases of true bacteriuria (2 45 ± 1 1 per cent) These 5 patients were afebrile and subjectively symptom free No pus cells were found in the urinary sediment

Table I *Bacterial Count*

Negative	< 10000 Organisms/ml	> 10000 Organisms/ml	Total
179	20	5	204

Table II *The Bacterial Strains Isolated*

Strain	< 10000 Organisms/ml	> 10000 Organisms/ml
E. coli	11	3
Klebsiella	–	1
Achromobacter	6	–
Alcaligenes fæcalis	1	–
Pseudomonas æruginosa	1	–
Staphylococcus aureus	–	1
Staphylococcus epidermidis	1	–
Total	20	5

Discussion

After parturition the mucosa of the bladder is œdematous and hyperæmic, and there are often submucous hæmorrhages The bladder is atonic and less sensitive evacuates incompletely, and usually contains residual urine All this favours the development of a urinary infection during puerperium (Ball 1951, Zinser, 1955 Eastman 1956)

ml, the patient was catheterized and a bacterial count of the catheterized urine taken The parturients who, for this or for some other reason, had to be catheterized in connection with delivery or during the puerperium were excluded from the series, as were patients treated with drugs in the maternity hospital, and patients who had complicated deliveries A few other cases also had to be discarded because no catheter specimen was taken, and two were excluded because they were discharged undelivered The remaining 204 cases were spontaneous deliveries with head presentation The mean age of the parturients was 25 5 ± 0 4 years 42 6 per cent were primiparae and 57 4 per cent multiparae

After the patients' external genitals and perineum had been washed with soap and water and the pubic hair shaved, the area of the urethral meatus was cleansed with 0 1 % Bradosol (Ciba) solution The parturient was asked to void urine The specimen was taken from mid-stream straight into a sterile test tube Before the parturient left the maternity hospital, usually on the seventh day *post partum*, she was catheterized with a metal catheter The specimens were immediately refrigerated and examined within 18 hours after collection Bacterial counts of both specimens were taken

The urinary deposit was examined in a cover glass preparation It was gram-stained and cultured on bromo-cresol purple lactose agar plate, 5 per cent sheep s blood agar plate, and a sheep's blood agar plate containing 0 08 per cent thallium acetate (for streptococci) The bacterial count was taken by the pour-plate method, mixing urine in nutrient agar The urine dilutions on the plates were 10^1, 10^2 – 10^8 The plates were incubated for 24 hours at 37° C In some cases where the colonies in the pour-plates were small, the count was re-checked after an incubation period of 48 hours The bacteria were identified as previously described (Virtanen and Kasanen, 1962) For the mid stream voided specimen over 100,000 bact /ml, (Jackson *et al*, 1958, Kass, 1960 b) and for the catheterized specimen over 10,000 bact /ml, (Boshell and Sanford, 1958, Merrit and Sanford, 1958, Davis *et al* 1959), were taken as indicating true bacteriuria

Wharton, 1947, Kass, 1960 b), and untreated infection is associated with abnormally high prematurity and neonatal mortality rates (Kass, 1960 a) For this reason the urine of every parturient should be bacteriologically examined on her leaving the maternity hospital or at the latest within 6–8 weeks at the follow up examination in the welfare centre

SUMMARY

The development of urinary infection during the puerperium was studied in a series of 204 normal parturients who had no infection on admission to the maternity hospital The possibility of iatrogenic infection was eliminated by taking the bacterial count prior to parturition on a mid stream voided specimen True bacteriuria developed in 5 cases (2 5 per cent) Asymptomatic bacteriuria was diagnosed in 38 out of 678 parturients (5 3 per cent) on admission The ratio between the incidence of bacteriuria developing during the puerperium and that detected prior to parturition was 1 2 A bacteriological investigation of the urine should be performed on all parturients on admission to and on discharge from the maternity hospital, or at the latest during the follow up examination

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In the present study, urinary infection during the puerperium was found to develop in 2.45 per cent of the cases. In the writer's previous papers (Virtanen, 1962 a and b), and in assembling the present material, true bacteriuria had been found, in a colony count of the catheter specimen of urine, in 36 of 678 parturients (5.3 ± 0.9 per cent) on admission to the maternity hospital. This difference is statistically significant ($0.001 < P < 0.01$). The mean age of the parturients was 25.4 years, and 46.5 per cent of them were primiparæ, hence the material is of comparable composition. It may be concluded, therefore, that the ratio between the incidence of urinary infection developing in puerperium and that diagnosed prior to parturition is 1 : 2.

The present study does not attempt to determine what proportion of the cases of bacteriuria diagnosed on admission had developed during pregnancy and how many had existed before pregnancy.

The incidence of 2.5 per cent found in the present study is considerably lower than the 15.9 per cent reported by Baird (1936 b) and the 21 per cent found by Jäämeri (1943) among Finnish parturients. These two investigations, however, were not carried out with the quantitative technique, and the figures therefore include the sampling contamination inevitable with routine methods. Baird's (1936 b) series also includeds the error due to iatrogenic infection resulting from catheterization. On the other hand, statistics for bacteriological examinations limited to cases showing subjective or clinical symptoms present a false picture of the incidence of puerperal urinary infection. The majority of cases escape detection, and a considerable proportion of those diagnosed represent a previous asymptomatic infection which becomes manifest during the puerperium.

Although bacteriuria cannot at present be identified with subclinical pyelonephritis (Kimmelstiehl *et al.*, 1961), a certain proportion of these patients will develop clinical signs of pyelonephritis. The exact proportion is not yet known (Jackson 1960, Kass 1960 b). Persistent urinary infection with very few or no symptoms may lead to chronic pyelonephritis with grave prognosis (Colby, 1959, Saphir and Cohen, 1959). There is a marked tendency to recurrence during later pregnancies (Baird, 1936 a

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BACTERIOLOGICAL COLONISATION OF INFANTS AND MOTHERS IN A MATERNITY UNIT

BY

HELGA LAURSEN

As part of a study on the colonisation and risk of infection by *Staphylococcus aureus* and other pathogenic micro-organisms in newborn infants and their mothers umbilical swabs from the infants and nasal swabs from both infants and mothers were taken routinely during a 12 month period

The purpose of the present paper is to report on the incidence of pathogenic organisms recovered from umbilical swabs in the infants and of staphylococcal colonisation of the nasal mucosæ of infants and mothers

Whilst staphylococcal colonisation of the nasal mucosa in this category of patients has been discussed and studied for many years, it is only during the last decade that attention has been focused on the problems related to the occurrence of staphylococci in the umbilical region

Isbister (1951) was one of the first who studied this problem She concluded that in spite of the fact that umbilical swabs frequently revealed pathogenic organisms severe infections were rare She expressed the view that umbilical cords which separate relatively late and are suppurating often harbour *Escherichia coli* or other Gram negative bacilli including *Pseudomonas æruginosa*, while staphylococci are often present in cases with only slight local changes but with more generalised reactions

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BACTERIOLOGICAL COLONISATION OF INFANTS AND MOTHERS IN A MATERNITY UNIT

BY

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As part of a study on the colonisation and risk of infection by *Staphylococcus aureus* and other pathogenic micro-organisms in newborn infants and their mothers, umbilical swabs from the infants and nasal swabs from both infants and mothers were taken routinely during a 12 month period

The purpose of the present paper is to report on the incidence of pathogenic organisms recovered from umbilical swabs in the infants and of staphylococcal colonisation of the nasal *mucosæ* of infants and mothers

Whilst staphylococcal colonisation of the nasal mucosa in this category of patients has been discussed and studied for many years it is only during the last decade that attention has been focused on the problems related to the occurrence of staphylococci in the umbilical region

Isbister (1951) was one of the first who studied this problem She concluded that in spite of the fact that umbilical swabs frequently revealed pathogenic organisms severe infections were rare She expressed the view that umbilical cords which separate relatively late and are suppurating often harbour *Escherichia coli* or other Gram negative bacilli, including *Pseudomonas æruginosa*, while staphylococci are often present in cases with only slight local changes but with more generalised reactions

Forshall (1957) collected six cases of umbilical sepsis with severe generalised reactions These included five with stahylococcal infections In 1957, Jellard reported that 60 per cent of swabs from the skin of the umbilical region yielded growths of staphylococci On the basis of her studies, Jellard concluded that the colonisation of the umbilicus was due to contact infection, as distinct from the nasal colonisation, which she thought was due to air borne infection

Fairchild *et al* (1958) performed serial studies of the bacterial content of the umbilicus in 211 infants Umbilical swabs yielded staphylococci at least once during the period of investigation in 210 cases Swabs obtained on the fourth or fifth day of life revealed *Staph aureus* in 86 per cent, hæmolytic streptococci in 62 per cent, *E coli* in 28 per cent, Klebsiella in about 10 per cent, *Ps æruginosa* in about 10 per cent, and negative findings in only 0 5 per cent

Similar studies in which attempts were made to reduce this colonisation by various hygienic measures have been reported by Coventry and Isbister (1951), Forfar and MacCabe (1958), Hirvensalo (1960) and Hurst (1960 a, b)

Newborn infants are colonised during the first few days of life by various pathogenic bacteria Staphylococci may often be demonstrated in the umbilicus and on the skin earlier than in the nose (Gillespie *et al*, 1958, Jellard, 1957), but the colonisation of the two former sites is often of shorter duration than in the nose The proportion of positive umbilical swabs fell to about 20 per cent on the tenth day of life (Gillespie *et al*, 1958, Simpson *et al*, 1960), while nasal carriage often persisted for from one to several years (Williams *et al*, 1960)

The risk of colonisation of newborn babies by resistant staphylococci during the hospital stay varies widely, and is influenced by a large number of factors, especially the presence or absence of an epidemic in the department at the time of examination and the predominance of certain staphylococcal strains During recent years, phage type 80/81 has played a conspicuous part in this respect

In addition, the hygienic standard of the department is of extremely great importance It is also of importance whether the

babies are placed in the same rooms as the mothers (rooming-in system) or in special nurseries together with other babies

Finally, the duration of the hospital stay must also be assumed to play a role, since a shorter stay in hospital will obviously reduce the risk of infection correspondingly For this reason, American investigators have tried to discharge patients as early as the third day after delivery (Kresky and Elias 1959), but here the danger of infection involved in a longer stay in hospital must be weighed against that of too early discharge of infants to environments where they may not receive adequate nursing In the clinic where the present investigation was performed the average length of the hospital stay is still from 8 to 10 days

From the numerous publications on the risk of colonisation by resistant staphylococci in maternity hospitals it may be mentioned that Farrer *et al* (1959) reported that 80 per cent or more of infants were nasal carriers on the eighth day of life Barber and Burston (1955) observed that 92 per cent were carriers and Cook *et al* (1958) claimed that nasal carriage was present in 100 per cent at the time of discharge from hospital In America Baldwin *et al* (1957) found that 30 per cent of infants were carriers at the time of discharge In contrast to these figures, Edmunds *et al* (1955) reported that positive nasal swabs were obtained in only 8 per cent of infants born at home or in hospitals using the rooming in system

In Denmark Helms and Stenderup (1961 a b) studied a similar series and found that 40 per cent of infants born in a maternity hospital carried staphylococci on the seventh day of life—most of the infants revealed hospital strains and only 9 per cent harboured the same type as their mothers

Obviously the mothers may also acquire resistant staphylococci during the hospital stay but do so only to a limited extent compared with their babies Edmunds *et al* (1955) found that maternal nasal carriage remained almost unchanged during the hospital stay (it increased from 28 7 to 30 7 per cent) Barber *et al* (1955) found that 49 per cent of the mothers were nasal carriers, and that contamination occurred in only 7 per cent during the hospital stay whereas Hutchison and Bowman (1957) reported that the rate of maternal nasal carriage increased from 47

to 63 per cent, and that carriage of resistant strains increased from 7 to 38 per cent

Personal Investigations

The maternity clinic in which the present study was performed receives about 2,700 maternity patients annually

The clinic is divided into three sections with rooms having from three to eight beds The newborn babies are placed at the foot end of the mothers beds In one of the sections there is a two-room nursery in which premature, sick and debilitated infants are placed immediately after delivery The delivery rooms are situated in a separate storey Each section is served by its own nursing staff assisted by midwife trainees, who periodically work either in the sections or in the delivery ward

The study extended over the period from August 14, 1959, to August 31, 1960 Umbilical swabs were taken on the day when the stump of the cord separated Nasal swabs were secured from the infants twice weekly and at the time of discharge, and from the mothers on admission, twice weekly and at the time of discharge Ordinary dry, sterile cotton swabs were used

The swabs were seeded on blood ager plates as soon as possible and then grown in fluid media, including infusion broth with 10 % NaCl If *Staph aureus* was found on the primary plate, it was isolated from there, and sensitivity tests were performed by the filter-paper disc method described by Jensen and Kiær (1948) as modified by Eriksen (1952), and Moltke and Eriksen (1957)

From all patients with positive swabs, at least one set of staphylococci was subjected to phage typing by K Rosendal, M D, of the State Serum Institute, Copenhagen Only coagulase-positive staphylococci were classified as pathogenic strains No staphylococcal epidemics occurred in the maternity clinic during the period of investigation

When the umbilical swabs yielded growths of pathogenic organisms other than *Staph aureus* especially coliforms (including *Ps æruginosa* and Proteus) and enterococci, the samples concerned were investigated as described in a previous study (Laursen, 1962)

Results

1 Umbilical Swabs

During the first half of the period of investigation, the umbilical cord was ligated with a sterile cotton thread and a sterile dressing was placed over the umbilical site From March 1, 1960, onwards, a newer method, in which a clamp is applied to the cord and the umbilical site left undressed, was employed The sterile metal clamps were applied as closely to the skin margin as possible immediately after delivery

During the first half of the period of investigation the umbilical region in all cases was dusted with Topicin powder (a mixture of

Table I *Survey of Micro-organisms Recovered from Umbilical Swabs Taken on the Day when the Cord Separated in two Groups of Infants in Whom the Cord (1) Was Tied with a Cotton Thread or (2) Closed with a Clamp*

Micro-organisms	Cotton Thread		Clamp		Total	
	No	%	No.	%	No	%
Staph. aureus	143	16 0	180	31 0	323	22 0
Ps aeruginosa	23	2 6	11	1 9	34	2 3
Lactose fermenting Gram negative[1]	36 } 47	5 3	54 } 71	12 3	90 } 118	8 0
Non-lactose fermenting Gram negative	11 }		17 }		28 }	
Proteus	12	1 3	8	1.4	20	1.4
Enterococci	55	6 2	42	7 3	97	6 6
Yeast cells	36	4 0	14	2 4	50	3 4
Other pathogenic micro-organisms	2 (pneumococci)		1 (haemol streptoc)		3	
Other (non pathogenic) micro-organisms	273 }	69 0 {30 6	144 }	52 6 {24 9	417 }	62 5 {28 3
No growth	343 }	{38 4	160 }	{27 7	503 }	{34 2
Total number of umbilical swabs	893		578		1471	
Total number of pathogenic strains	318		327		645	
More than one pathogenic strain per swab	23		19		42	

[1] bacilli

0 5 % neomycin sulphate and 1 % bacitracin in an inert powder base), during the second half, dusting with Hibitane powder (consisting of *1 % chlor-hexedine in sterile talcum*) was used in one section of the clinic, while Topicin was still used in the other

The results of the umbilical cultures are shown in Table I

In addition to the total number of positive swabs, Table I also shows the incidence of micro-organisms isolated from umbilical swabs when the cord was ligated with a cotton thread or was closed with a clamp

The general impression is that fewer swabs yielded pathogenic organisms after the former method of umbilical closure (cotton thread plus dressing) than after the latter (clamp, no dressing), which is in conformity with the results reported by Hunting ford *et al* in 1961

Incidentally, as compared with those stated in the literature, the present results are encouraging *Staph aureus* was present in 22 per cent, various Gram-negative bacilli in about 12 per cent, and enterococci in about 7 per cent Yeast cells were disclosed relatively often, *viz* in nearly 4 per cent

According to Vignec (1958) and Kozinn *et al* (1958), yeast cells play an appreciable part in skin affections in newborn infants and in oral thrush A reservoir of yeast cells in the um bilicus may therefore be of some pathogenic significance In agreement with *this four infants revealed napkin-area dermatitis* caused by yeast cells, all four cases proved refractory to treatment and persisted for long periods

Other pathogenic micro-organisms (pneumococci and hæmolytic streptococci) were found in only a few cases Other micro-organisms' (mainly *Staph albus*, diphteroid bacilli and *B subtilis*) were not further differentiated as they were considered to be *of no pathogenic significance*

It is of interest to note that none of the infants observed during the 12 month period of investigation presented any clinical signs of umbilical infection

Table II shows the incidence of positive swabs from infants in whom the umbilicus was treated with either Topicin or Hibitane powder, in all these cases, umbilical metal clamps were employed

Dusting of the umbilical region with Topicin was used because

Table II Survey of Micro-organisms Recovered from Umbilical Swabs Obtained from Infants in Whom the Cord Was Closed with a Clamp, and in Whom Dusting with either Topicin or Hibitane Was Used

Micro-organisms	Topicin powder No	%	Hibitane Powder No	%	Total No	%
Staph. aureus	145	29.8	35	38.0	180	31.0
Ps æruginosa	8	1.6	3	2.2	11	1.9
Lactose fermenting Gram negative bacilli	36 } 50	10.3	18 } 21	21.7	54 } 71	12.3
Non lactose fermenting Gram-negative bacilli	14		3		17	
Proteus	4	1.0	4	4.3	8	1.4
Enterococci	36	7.4	6	6.5	42	7.3
Yeast cells	14	2.9	0		14	2.4
Other pathogenic micro-organisms	1 (hæmol streptoc)				1	
Other (non pathogenic) micro-organisms	118 } 54.9	24.3	26 } 40.2	28.3	144 } 52.6	24.9
No growth	149	30.7	11	12.0	160	27.7
Total number of umbilical swabs	486		92		578	
Total number of pathogenic strains	258		69		327	
More than one pathogenic strain per swab	5		14		19	

an appreciable fall in the incidence of infections in both infants and mothers had been observed in another Danish maternity department after the introduction of this treatment (Kærn, 1959)

Hibitane dusting was given a trial after the publication of reports by Gillespie *et al* (1958) and Simpson *et al*, 1960) in which they stated that they had observed a considerable reduction both in the tendency to colonisation and in the incidence of infections by *Staph aureus* among infants and mothers after dusting of the umbilical region with hexachlorophene

It was not possible to obtain a true control series in which no dusting powder was used and this to some extent, detracts from the value of the results in the control group

It appears from Table II that from a bacteriological point of

view, the use of Topicin gave appreciably better results than were obtained by Hibitane, both as far as colonisation by *Staph aureus* and Gram-negative bacilli was concerned On the other hand none of the swabs from Hibitane-treated infants yielded any growth of yeast cells

In all four cases of napkin-area dermatitis, Topicin dusting of the umbilical region had been used

As regards the closer analysis of the pathogenic bacteria isolated from the umbilical swabs, the incidence of staphylococci is considered in the section on this micro-organism All other pathogenic bacteria were also studied with regard to lactose fermentation and sensitivity to various antibiotics and sulphathiazole Apart from *Ps æruginosa*, few resistant strains were revealed, which is in agreement with the fact that the standard antibiotic therapy of the clinic consisted in administration of penicillin, occasionally supplemented by streptomycin, whereas broad-spectrum antibiotics were used only in exceptional cases

2 *Studies on Staphylococci*

The series comprised umbilical swabs from 1,471 infants, including 323 with staphylococcal colonisation at the time of investigation Nasal swabs were performed in 2,165 infants and 2,531 mothers

At the time of discharge, 973 infants were nasal carriers of staphylococci, while cultures failed to reveal nasal carriage of pathogenic staphylococci in 1,103 infants In 89 cases, one or more nasal swabs yielded a growth of staphylococci, but the swabs obtained at the time of discharge were negative Thus, the presumed risk of nasal carriage was 46 9 per cent (max 49 1 per cent, min 44 9 per cent)

Nasal carriage of *Staph aureus* at the time of discharge was demonstrated in 1,130 mothers, while nasal swabs failed to reveal the presence of staphylococci in 1,401 mothers, but 224 of these cases were questionable, since only one swab had been obtained either immediately on or shortly after admission, i e, the nasal swabs were unquestionably negative at discharge in 1,177 cases Nasal colonisation with staphylococci on the day of discharge was thus demonstrated in an average of 49 0 per cent

(max 53 5 per cent min 44 6 per cent) of the mothers Among 1,890 nasal swabs secured immediately on admission 1,230 samples showed no pathogenic staphylococci, while 677 patients were nasal carriers on admission

The resistance pattern of the staphylococci isolated from both umbilical and nasal swabs is shown in Table III

Table III *Pattern of Resistance of the Strains of Staph aureus Isolated from Infants and Mothers*

Sensitivity of Isolated Strains	Isolated from Umbilical Swabs		Isolated from Nasal Swabs			
	Infants		Infants		Mothers	
	No	%	No	%	No.	%
P	226	67 8	827	71 8	486	45 0
Sens	70	20 8	249	21 6	533	49 4
PS	33	9 8	63	5 8	50	4 6
S	1		1		3	
PST	3		8		2	
PSC	0		2		1	
PTC	0		1		1	
PT	2		1		4	
T	1		0		0	
Total	336		1 152		1 080	
More than one pathogenic strain per swab	13		80		24	

Key to abbreviations
- P resistant to penicillin
- Sens sensitive to the antibiotics tested
- S resistant to streptomycin
- T resistant to tetracyclines
- C resistant to chloromycetin

It appears that among the infants 336 strains were isolated from umbilical swabs (two strains in the same swab were observed in 13 cases) and 1 152 strains from nasal swabs (each swab revealed more than one strain in 80 cases) In five cases, the sensitivity of the staphylococci changed in the nasal swabs obtained from the

view, the use of Topicin gave appreciably better results than were obtained by Hibitane, both as far as colonisation by *Staph aureus* and Gram-negative bacilli was concerned On the other hand none of the swabs from Hibitane-treated infants yielded any growth of yeast cells

In all four cases of napkin area dermatitis, Topicin dusting of the umbilical region had been used

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Both as far as infants and mothers are concerned it is a strikingly small fraction which are—or become—carriers of staphylococci which are resistant to penicillin and streptomycin, and only very few acquire staphylococcal strains which are resistant to broad spectrum antibiotics The studies did not reveal any strains which were resistant to erythromycin

The distribution of the phage types of the staphylococcal strains appears from Table IV

Table IV *Distribution of the Phage Types of the Staphylococcal Strains*

Phage Types	Isolated from Umbilical Swabs		Isolated from the Nasal Swabs			
	Infants		Infants		Mothers	
	No	%	No		No	%
3A	61	18 1	293	25 4	203	17 7
80	45	13 4	118	10.2	138	12 1
187	18		43		29	
Group I (except type 80)	20		65		133	
Group II (except type 3A)	45	13 4	174	15 1	135	11 8
Group III	96	28 6	276	23 9	239	20 9
Group IV	0		1		1	
Miscell +non identifiable (except type 187)	10		67		102	
Non-typable	41		115		164	
Total	336		1152		1144	

The phage types were classified according to the principles of Rosendal (1959) and Eriksen and Rosendal (1960), apart from the fact that type 3A was segregated from group II, because this type—contrary to findings in most other maternity hospitals—was very frequent in our clinic As in most other reports from the literature type 80 was segregated from group I, and certain closely related strains were included under type 80, vi- type 81 and the phage type patterns 80/81 52/52A/80, and 52/52A/80/81

It appears from the table that there was a very large number of strains belonging to type 3A, in particular there was a distinct

same infant, viz Sens[1] →P, 2, P→Sens, 2, PS→P, 1 However, as these changes are numerically insignificant as compared with the entire series, these ten strains are included in Table III

In the mothers, a total of 1,154 strains of Staph aureus were isolated (two strains were present in the same swabs in 24 cases) As shown below, shifts in the resistance pattern occurred in 74 cases, for which reason these are not included in Table III

	No of cases
Sens → P	45
P → Sens	24
PS → P	1
P → PS	2
PS → Sens	1
S → Sens	1
	74

Sensitivity tests in the 677 patients who were staphylococcal carriers on admission showed that 277 strains (or 40 9 per cent) *were resistant to penicillin, 32 (or 4 7 per cent) were resistant* to both penicillin and streptomycin, one was resistant to penicillin and tetracyclines, and three were resistant to streptomycin In this connexion especially it should be noted that there was only a slight difference in the carrier rates of penicillin resistant staphylococci on admission and at the time of discharge (an increase from 40 9 per cent to 45 0 per cent), and that during the hospital stay only 18 mothers acquired staphylococci which were resistant to penicillin and streptomycin

Another striking feature is that while about one half of the mothers were discharged with sensitive staphylococci, 70 per cent of the infants harboured penicillin resistant staphylococci at this time This is in agreement with the statements in the literature that the infants are *discharged with hospital acquired staphylococci*, whereas the mothers largely retain the nasal flora which are present on admission

[1] For key to abbreviations, see Table III

Table VI *Pattern of Resistance of Type 3A Staphylococci*

Sensitivity of Strains	Isolated from Umbilical Swabs	Isolated from Nasal Swabs			
	Infants	Infants		Mothers	
	No	No	%	No	%
P	58	269	91 8	154	75 9
Sens	3	20	6 8	45	22 1
PS		4		3	
PT				1	
Total	61	293		203	

A similar analysis of type 3A organisms shows that this type is almost exclusively penicillin resistant.

An analysis of the cases in which infant and mother were carriers of the same type of staphylococci is presented in table VII

Table VII Staphylococcal Strains of Identical Phage Type and Resistance Pattern Isolated from the Nasal Mucosa in Infant and Mother

Phage Types	No	%	Infant Revealed Same Type as Mother on Admission	
			No	%
3A	66	23 7	22	(23 4)
80	37	13 3	16	(17 0)
187	16		10	
Group I (except type 80)	16		9	
Group II (except type 3A)	32	11 5	16	(17 0)
Group III	67	24 1	32	(34 0)
Group IV	1		1	
Miscell + non-identifiable (except type 187)	15		5	
Non typable	28		13	
Total	278	26.2	124	(11 7)

It is seen that at discharge about one quarter of the infants were nasal carriers of the same type of staphylococci as their mothers whereas only 124 infants had the same type as had been isolated from their mothers on admission, *i e* it must be presumed that these mothers had transmitted the micro-organisms to

preponderance of these strains in nasal swabs from the infants Another striking feature is that the number of type 80 organisms was relatively low, *viz* 10 and 13 per cent in nasal and umbilical swabs from the infants and 12 per cent in the mothers Groups I, II and III did not present any striking features although it has often been stated that group III has a preponderance in maternity departments Incidentally, it is worth noticing that a large number of variations in the phage pattern were present A comparison of Tables III and IV shows that the number of type 80 organisms was considerably higher than that of strains which were resistant to both penicillin and streptomycin, although this resistance pattern is usually reported as being associated with type 80/81 This is particularly evident in the organisms isolated from nasal swabs A further analysis of type 80 organisms only is therefore given in Table V

Table V *Pattern of Resistance of Type-80 Staphylococci*

Sensitivity of Strains	Isolated from Umbilical Swabs	Isolated from Nasal Swabs			
	Infants	Infants		Mothers	
	No	No	%	No	%
P	12	43	36 6	24	17 4
Sens	11	28	23 7	73	52 9
PS	22	46	39 0	38	27 5
S				1	
PST				1	
PSC		1		1	
Total	45	118		138	

It is seen that the infants revealed a considerable difference in the distribution of the resistance pattern of this phage type in umbilical and nasal swabs, about 50 per cent of the strains from umbilical swabs were resistant to penicillin and streptomycin, as compared with only 39 per cent from the nasal swabs Strangely enough, 50 per cent of the strains isolated from the mothers were sensitive to all antibiotics, presumably indicating that most of the strains originated from outside the clinic

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	Infants	Infants		Mothers	
	No	No	%	No	%
P	58	269	91 8	154	75 9
Sens	3	20	6 8	45	22 1
PS		4		3	
PT				1	
Total	61	293		203	

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Table VII *Staphylococcal Strains of Identical Phage Type and Resistance Pattern Isolated from the Nasal Mucosa in Infant and Mother*

Phage Types	No	%	Infant Revealed Same Type as Mother on Admission	
			No	%
3A	66	23 7	22	(23 4)
80	37	13 3	16	(17 0)
187	16		10	
Group I (except type 80)	16		9	
Group II (except type 3A)	32	11 5	16	(17 0)
Group III	67	24 1	32	(34 0)
Group IV	1		1	
Miscell + non identifiable (except type 187)	15		5	
Non typable	28		13	
Total	278	26 2	124	(11 7)

It is seen that at discharge about one quarter of the infants were nasal carriers of the same type of staphylococci as their mothers whereas only 124 infants had the same type as had been isolated from their mothers on admission i e , it must be presumed that these mothers had transmitted the micro-organisms to

their babies In view of the fact that the rooming-in system was employed in the clinic, this figure seems to be relatively low

The distribution of the types is roughly the same as in the total series, but as the percentages are calculated from relatively small figures, these are given in parentheses This is also done in Table VIII, which shows the distribution of the phage types revealed in infants in whom staphylococci were isolated from both nasal and umbilical swabs

Table VIII *Staphylococcal Strains of Identical Phage Type and Resistance Pattern Isolated from Umbilical and Nasal Swabs in the Infants*

Phage Types	No	%
3A	26	(27 0)
80	10	(10 4)
187	5	
Group I (except type 80)	8	
Group II (except type 3A)	16	(16 7)
Group III	25	(26 0)
Group IV	0	
Miscell +non identifiable (except type 187)	2	
Non typable	4	
Total	96	(29 7)

Among the 336 phage-typed staphylococcal strains isolated from umbilical swabs, only those exhibiting both the same type and resistance pattern were classified as identical

The comparatively slight agreement between the results mi *litates against the assumption of auto-infection and is, if anything,* rather in favour of the theory advanced by Jellard (1957), *viz* that the modes of infection of the umbilicus and nose in newborn infants are fundamentally different

Discussion

As already pointed out, umbilical swabs were obtained in 1,471 newborn infants on the day the cord separated, *i e* usually on the fourth, fifth or sixth day of life This time was chosen because it

must be assumed that this period affords the best conditions of growth for micro-organisms, as was also shown by Fairchild *et al* (1958)

In the entire series, growth of *Staph aureus* was seen in 22 per cent, various Gram negative bacilli in nearly 12 per cent, enterococci in nearly 7 per cent, yeast cells in 4 per cent, and pneumococci and hæmolytic streptococci in only a few cases, while no growth at all or growth of presumed non pathogenic organisms was observed in about 63 per cent. When compared with those reported in the literature, these results were on the whole, satisfactory

During the entire period of investigation the umbilical region was dusted with antibacterial powder, which may explain the relatively low incidence of pathogenic micro-organisms

During the first half of the period the umbilical cord was tied with a cotton thread and the site covered with a sterile dressing, while a clamp was applied to the cord and the umbilical site left undressed during the second half of the period The analysis of the series showed that the conventional method employing a thread and a sterile dressing gave the lowest incidence of colonisation, which is in agreement with the results reported by Huntingford (1961)

On the other hand, Table II shows that there was less bacterial growth after treatment of the umbilical site with Topicin powder than after dusting with Hibitane However, this did not apply to contamination with yeasts, since the 50 infants in whom umbilical swabs revealed yeast cells had all been treated with Topicin powder In the four cases of severe napkin area dermatitis due to infection by yeast cells, the umbilical region had also been treated with Topicin

The studies of large series reported by Gillespie *et al* (1958) and Simpson *et al* (1960) showed that dusting with hexachlorophene of the umbilical region and other exposed parts of the trunk result in a considerable reduction in staphylococcal cross-infection both as far as carriage and incidence of clinical infections are concerned

In agreement with this, Jellard (1957) demonstrated that painting with Triple Dye (a mixture of brilliant green crystal

violet and proflavine) resulted in a diminished tendency to staphylococcal colonisation

Judging from the literature, it seems to be serious to omit treatment with antibacterial substances entirely—apart from very short experimental periods The results of the present study are also in favour of the use of such substances On the other hand, the problem as to what is the substance of choice in reducing the growth of all pathogenic micro organisms still awaits solution

It appears from this report that nearly one half of the infants and mothers were nasal carriers of *Staph aureus* at discharge As compared with the numerous reports in the literature (Barber and Burston, 1955, Hurst, 1960 a, b, Jellard, 1957, Monroe and Markham, 1958), this result is relatively satisfactory and in harmony with the fact that staphylococcal epidemics have not occurred in the clinic for several years

In the infants, particularly penicillin-resistant, hospital-acquired strains were recovered About 70 per cent of the strains isolated from the infants were penicillin-resistant, and only about 20 per cent were *fully sensitive to all antibiotics—both in umbilical and* nasal swabs

On the other hand, the mothers often retained—or acquired—a flora which differed from the hospital strains, as manifested by the fact that only about 45 per cent of the staphylococcal strains isolated from nasal swabs in the mothers, were *penicillin-resistant*, while about 50 per cent were fully sensitive

Some mothers became carriers during their hospital stay (an increase from about 36 to 49 per cent), but it must be supposed that they often were colonised by staphylococci originating from fellow-patients This is in agreement with the fact that the increase in penicillin resistant strains from admission to discharge was only slight (from about 40 to 45 per cent)

Most authors have observed similar or higher frequencies of resistant strains The figures reported by Helms and Stenderup (1959, 1961 a, b) from another maternity hospital are of the same order as those of the present study, while the occurrence of resistant strains is far more frequent in studies from other countries In 1955, Barber and Burston reported that up to 92 per cent of the infants were colonised during the hospital stay, including 89 per cent carriers of resistant staphylococci

In the present series only relatively few of the infants and mothers were colonised by strains resistant to penicillin and streptomycin, and only an insignificant number acquired multi-resistant staphylococci

An analysis of the distribution of the phage types shows that the infants were mainly colonised by strains belonging to type 3A (about 25 per cent) and group III (about 24 per cent), while the staphylococci isolated from the mothers were widely scattered over the groups However, there was a slight preponderance of group III (about 21 per cent), and type 3A was isolated from about 18 per cent of the mothers Of the latter, one quarter were sensitive to penicillin, *i e*, they could not be considered to belong to the hospital strain 3A

Type 80/81 represented only a minority in this series, *viz* 11 per cent of the total number of staphylococcal strains isolated from the infants and 12 per cent in the mothers Also here, there was a considerable difference in the two categories of patients Of type 80/81 staphylococci from the infants 42 per cent were resistant to both penicillin and streptomycin and only 24 per cent were sensitive, while 53 per cent of the strains isolated from the mothers were sensitive to the antibiotics studied

It is not a feature specific for our clinic that group III was relatively frequently seen in the present series Other authors have found that certain types belonging to group III were predominant in the maternity clinics investigated (Hutchison and Bowman 1957, Williams, 1959 Williams *et al*, 1960)

Finally, it was seen that at the time of discharge both mother and baby were nasal carriers of identical staphylococci in about one quarter of the cases *viz* in 278 pairs of mothers and infants, but only in 124 of these pairs was the type revealed at discharge the same as that isolated from the mother on admission This seems to show that when the rooming in system is used colonisation of the infant occurs not from the mother but from other sources The infants are, of course also handled by the nurses when this system is employed but it is probably of importance that only a maximum of 6 to 8 infants are placed together with their mothers in one large room so that the chances of cross colonisation are restricted

Few reports on the results of the rooming-in system are available in the literature Farrer *et al* (1959) subjected this system to a trial, together with other measures, during an epidemic and found that rooming-in was the most important measure in breaking the chain of infection In an epidemic occurring in another maternity clinic in this country, Tulinius and Rosendal (1956) also obtained good results by employing the rooming in system, and Hurst (1960 a, b) suggested that this measure was a safe method for breaking the circle of staphylococcal cross infection

Incidentally, numerous measures aiming at diminishing staphylococcal colonisation in newborn infants have been suggested during recent years Thus, local or general administration of various antibacterial drugs has been recommended and studied erythromycin (Kresky and Elias, 1959, Schaffer *et al*, 1956), Naseptin, *i e*, a complex preparation consisting of chlorohexedine and neomycin in ointment base (Jennison and Komrower, 1961), hexachlorophene for dusting, painting and for bathing (Baldwin *et al*, 1957, Gillespie *et al*, 1958, Shaffer *et al*, 1956, Simpson *et al* 1960)

The local treatment just mentioned consisted of nasal application to the infants and nasal carriers among the staff and application of the antibacterial preparation to the hands of the nurses in order to prevent transmission from baby to baby

It must be emphasised that one of the causes of the relatively satisfactory results obtained in the present series was that the regimen of aseptic precautions was strictly enforced in the ward included in the investigation Hand washing was obviously imperative before each individual baby was handled by the nurses, each patient had her own utensils, bed clothes, clothing, etc were sterilised before they were used for the next patient The floors were carefully washed, but oiling was not used As far as possible, the large rooms were emptied and carefully cleaned at frequent intervals before new patients were admitted

As far as possible, all infected patients were subjected to bacteriological studies including sensitivity tests, and then usually treated with penicillin, occasionally supplemented by streptomycin, while broad-spectrum antibiotics were used very sparingly

The results of this study show that these simple, inexpensive and easily practicable measures are of great value

SUMMARY AND CONCLUSIONS

The results of bacteriological studies performed in a maternity clinic during a 12 month period are presented Umbilical swabs were obtained in the infants on the day when the cord separated, and nasal swabs were secured in the infants twice weekly and at discharge and in the mothers on admission, twice weekly and at discharge

A total of 1,471 umbilical swabs were studied The growth pattern was as follows no growth or growth of only non pathogenic micro-organisms, about 63 per cent, *Staph aureus*, 22 per cent, various pathogenic Gram negative bacilli, about 12 per cent, enterococci, about 7 per cent, yeast cells, 4 per cent, and pneumococci and hæmolytic streptococci in only a few cases

During the first half of the period of investigation the umbilical cord was ligated with a cotton thread and covered with a sterile dressing, during the second half a metal clamp was used, and the umbilical site was left undressed. The umbilical region was dusted with either Topicin or Hibitane

It appeared from the study that less growth of pathogenic micro-organisms occurred when a cotton thread and sterile dressing on the umbilical site were employed, and also when the umbilical region was dusted with Topicin instead of Hibitane However the latter statement does not apply to the occurrence of yeast cells which in all 50 cases in which these were observed originated from infants treated with Topicin

The results of the nasal swabs showed that nearly one half of 2 165 infants (average 47 per cent) were nasal carriers of staphylococci at the time of discharge, mainly with penicillin resistant strains (about 70 per cent), and that among 2 531 mothers nasal carriage whilst in hospital increased from about 36 to 49 per cent, while the incidence of penicillin resistant strains only increased from 40 to 45 per cent This seems to indicate that the mothers retained—or acquired—a nasal flora which differed *from* that usually prevalent in the hospital

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Finally my best thanks are due to the members of the nursing staff of Maternity Clinic B, Rigshospitalet for their kind assistance accorded to me during the performance of the investigation

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Only a few mothers and infants were colonised with staphylococci which were resistant to streptomycin and penicillin (about 10 per cent and 6 per cent from umbilical and nasal swabs respectively in the infants, and about 5 per cent in the mothers), and only very few were colonised with multi-resistant staphylococci

Phage typing showed that the infants were mainly colonised with type 3A (25 per cent) and strains belonging to group III (24 per cent), while type 80/81 did not play a conspicuous part (average 11 per cent, *viz* 13 per cent and 10 per cent from umbilical and nasal swabs, respectively)

Identical strains were recovered from umbilical and nasal swabs from the same infant in nearly 30 per cent (in 96 out of 323 cases) This observation provides evidence against the theory of auto-infection and is in favour of the assumption that the modes of colonisation on the umbilicus and nasal mucosa are fundamentally different

The occurrence of staphylococci in the mothers was to a greater extent, scattered over all groups, although 21 per cent of the mothers were carriers of staphylococci belonging to group III, type 80/81 was revealed in 12 per cent of the cases It appeared that about one half of the strains belonging to type 80 isolated in the mothers were sensitive to the antibiotics studied

As the rooming-in system was used in the maternity clinic studied, the extent to which both mother and infant were carriers of identifical strains at discharge was investigated This proved to be the case in about one quarter of the pairs of mothers and infants, but only in 124 of these 278 pairs was the strain recovered identical with the type obtained in the mother on admission As the entire series shows the mothers do not often transmit their bacterial flora to their babies, even when the rooming in system is employed

The low over all incidence of colonisation is persumably due to the fact that a maximum of 6 to 8 babies were placed together with their mothers in large rooms as distinct from the crowding together of a large number of infants in a nursery

The strict aseptic precautions adhered to in the clinic must also be supposed to have been a factor contributing to the low incidence of colonisation

The use of antibacterial substances was restricted to the afore mentioned dusting of the umbilical region and appropriate anti biotic treatment of infected patients

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From the Department of Radiology (Professor F Knutsson), University Hospital Uppsala Sweden

CORONAL CLEFT VERTEBRA IN FŒTUSES OF MALE SEX

BY

STIG FAGERBERG

The sex of fœtus may be determined antenatally by a study of the sex chromatin in the nuclei of desquamated skin cells in the amniotic fluid (Trasler *et al* 1956, Makowski *et al*, 1956, James, 1956, Dewhurst, 1956, Fuchs *et al*, 1956, 1960) There is no recorded radiological method for antenatal sex deter mination However, in certain exceptional cases it is possible to forecast with a relatively high degree of certainty that the fœtus is male using radiological methods This is based upon the demonstration of certain deviations from the normal in the ossifica tion of the vertebral bodies (Rowley, 1954, Stewart *et al*, 1957)

In the cartilage stage of the vertebral bodies there is a bilateral symmetry with two lateral cartilage nuclei separated by the chorda dorsalis and the perichordal septum Both halves of the cartilage unite and when ossification sets in the symmetry changes to a dorso-ventral direction with an anterior and a posterior bone nucleus These nuclei in turn unite at about the fourth fœtal month This account of the vertebral development is given by Junghanns and is based upon histological studies of fœtuses of different ages and the reconstruction of a number of malforma tions within this skeletal region Ossification changes can ac cordingly give rise to an anterior and a posterior half vertebra or, if both the nuclei fail to fuse together to a "cleft" formation in the frontal plane The space between the bone nuclei is filled up with

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cartilage and appears in the rœntgen film as a radiolucent zone or as a cleft This anomaly is called "coronal cleft vertebra' in the English literature, in order to differentiate it from the better known cleft in the sagittal plane It has previously been described by several authors The sex relationship, however, has only recently been pointed out Rowley (1954) and Stewart et al (1957), showed the male dominance of the condition These authors regarded this ossification change as an anomaly without any pathological significance

The purpose of this investigation has been to study the frequency and significance of this malformation in a personal series

Material

The series consisted of two groups

Group I consisted of 400 obstetrical patients who underwent *radiological examination for widely different indications during* the last two months of pregnancy As a routine in all these investigations a frontal film had been taken with the woman in the prone position This always gave a picture of the whole fœtus A lateral view of the fœtus was often obtained with this technique, which *is*, of course, necessary to assess the occurrence of coronal cleft vertebra 150 cases satisfied this requirement and have constituted the basis of this study

Group II In order to estimate the frequency of this anomaly in a normal series 150 healthy, newborn children were examined with a true lateral view of the vertebral column

Results

Group I Of the 150 cases with suitable views ten *showed a* coronal cleft vertebra, nine boys and one girl The distribution of the anomaly in the different regions of the vertebral columns is shown in *Table I* The affected vertebral body is broadened sagitally and divided by the cleft into a larger anterior and a smaller posterior part (Figs 1 and 2) The cleft can be complete or partial, with overbridging bone substance in the upper or lower region The anomaly can also occur mainly as a central

Table I *Details of the Cases in Group I*

Case No	Mother	Radiological Findings	Child	Autopsy Findings
1	I parous 28 years Healthy	Dead fœtus Coronal cleft of L4	Dead boy Weight 3590 gm Length 53 cm	Macerated fœtus
2	III parous 28 years Toxæmia of pregnancy	Coronal cleft of L2—4	Dead boy Weight 1250 gm Length 40 cm	Macerated fœtus
3	III parous 32 years Rh-immunization	Coronal cleft of L2—3	Dead boy Weight 3430 gm Length 52 cm	Erythroblastosis fetalis+subarachnoid hæmorrhage
4 (Fig 1)	I parous 20 years Healthy	*Coronal cleft* of L2—5	Boy Weight 1770 gm Length 43 cm Dead 2 days after delivery	Premature fœtus+meconium ileus
5	III parous 34 years Rh-Immunization	Coronal cleft of D3 L2—3	Boy Weight 3100 gm Length 50 cm Erythroblastosis fetalis	—
6	I parous 26 years Toxæmia of pregnancy	Coronal cleft of L3—5	Boy Weight 2880 gm Length 49 cm Erythroblastosis fetalis	—
7	IV parous 27 years Healthy	Coronal cleft of L2—4	Boy Weight 4150 gm Length 51 cm Healthy	—
8 (Fig 2)	I parous 25 years Healthy	Coronal cleft of D3 D6 D8—9 L2	Boy Weight 3470 gm Length 51 cm Amblyopia	—
9 (Fig 4)	I parous 24 years Healthy	Coronal cleft of D12 L2—5	Boy Weight 3630 gm Length 47 cm Healthy	—
10 (Fig 3)	I parous 30 years Toxaemia of pregnancy	Coronal cleft of L4—5	Girl Weight 2810 gm Length 47 cm Healthy	—

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Fig. 2 Case 8 Lateral view of the spine before birth Coronal clefts in D3, D6 D8—9 and L2

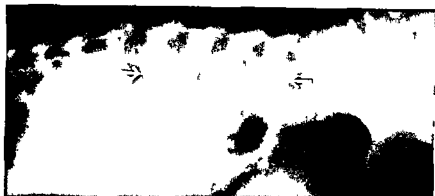


Fig 1 Case 4 Lateral view of lumbar spine at birth Coronal clefts in L2—5 (between the arrows)

radiolucent zone in the vertebral body and it is then less con spicuous (Fig 3)

If the series is analysed with special reference to the mothers and the children, several interesting features appear apart from the sex relationship, *Table I* A deviation from the normal is found in five mothers, that is 50 per cent (toxæmia of pregnancy and rh-immunization) Concerning the children, four died *before, at or shortly after delivery (maceration, erythroblastosis* fetalis plus subarachnoid hæmorrhage and prematurity with me conium ileus) whilst three presented morbid features (erythro blastosis fetalis, amblyopia) Three children were healthy

No other malformations of the skeleton were demonstrated

As regards the ossification defect in the vertebra it appears that a rapid consolidation takes place One of the healthy children has been reexamined after six months Only a slight suggestion of the previously observed marked clefts remained (Fig 4) This is in agreement with both Rowleys, Knutssons and Fawcitts observations, as well as with the fact that these changes are never found in the adult

Group II The cases in the first group are selected in that all cases, for some clinical reason required radiological investigation and, only those giving a lateral view of the vertebral column could be *interpreted* No real estimate of the frequency of the malformation can therefore be obtained from this series Of the



A B

Fig 4 Case 9 Lateral view of lumbar spine A Before birth. Coronal clefts in D12 and in L2—5 B Six months after birth. The cartilage zones in D12 and L2—3 have disappeared. Small remnants of the clefts in L4—5



Fig 3 Case 10 Lateral view of lumbar spine before birth Partial cleft of L4 and a very small central translucency of L5

150 children in the second group only one, a boy, showed a coronal cleft vertebra, in a lumbar vertebral body The frequency of the malformation in a normal series appears therefore, to be less than 1 per cent

Discussion

Ossification of the skeleton commences earlier and proceeds more quickly in girls than in boys Bone nuclei appear at an earlier stage and the epiphyseal lines disappear sooner in girls than in boys Therefore, one could draw the conclusion that the vertebral anomaly is only a consequence of delayed ossification and therefore most likely to be found in a male child It is difficult, however, to equate this conclusion with the large discrepancy in the occurrence of the anomaly between the two sexes The increased mortality and morbidity in the series indicates a possibly more complex ætiology which, because of the sex correlation, may involve the sex chromosomes Previously reported series support this assumption Thus, Rowley s series of 31 boys and three girls of which 28 are reported in greater detail, show no less than 13 dead and two seriously ill children Of the three cases reported by Knutsson, all boys, one was dead and two premature children were living Cohen *et al* has described a number of other non-skeletal malformations with increased mortality in a series of 20 cases with vertebral changes

Nilsson O Kottmeier H L, and Tillinger K G Acta obst et gynec scandinav 42 73 1963

From the Department of Histology Karolinska Institutet (Associate Professor L Gyllensten) the Department of Gynæcology Radiumhemmet (Docent H L Kottmeier) and the Department of Women s Diseases (Professor U Borell)

SOME DIFFERENCES IN THE ULTRASTRUCTURE OF NORMAL AND CANCEROUS HUMAN UTERINE EPITHELIUM

BY

O NILSSON H L KOTTMEIER AND K G TILLINGER

The electron microscopic appearance of the cyclical changes in the uterine gland epithelium was first reported by Borell Nilsson and Westman in 1959 Several workers have since contributed to our knowledge of this tissue (for references see Nilsson 1962[1 2]) The view obtained of the normal ultra structure of the uterine epithelium afforded a basis for studies on the ultrastructure of the pathological conditions in this epithelium Thus the appearance of hyperplastic endometrium (Wessel 1961) and of adenocarcinoma (Sirtori 1960 Sirtori and Morano 1961 Nilsson 1962) was described The present paper demonstrates some of the ultrastructural differences which are present between normal and cancerous uterine epithelium

Material and Methods

The specimens of the normal endometrium were obtained with a biopsy curette from 9 women in the follicular phase and from 8 women in the luteal phase This material and the methods are described and discussed in earlier papers (Nilsson 1962 [-])

The specimens of the cancerous endometrium were obtained with a biopsy curette from 1 woman in the late secretory phase and from 3 women in the menopause This material and the methods are described and discussed in an earlier paper (Nilsson 1962[3])

of the type under consideration The sex distribution, however, is not given for this series

SUMMARY

In a series of 150 obstetrical radiological investigations, the occurrence of so-called coronal cleft vertebra has been studied

The frequency of this anomaly is low If it is shown in a fœtus during the last two months of pregnancy, then it is more than 90 per cent probable that the fœtus is of male sex Such an anomaly has no pathological significance in itself, but it may occur in association with other more serious abnormalities The anomaly *disappears during the first year of life*

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SOME DIFFERENCES IN THE ULTRASTRUCTURE OF NORMAL AND CANCEROUS HUMAN UTERINE EPITHELIUM

BY

O NILSSON H L KOTTMEIER AND K G TILLINGER

The electron microscopic appearance of the cyclical changes in the uterine gland epithelium was first reported by Borell Nilsson and Westman in 1959 Several workers have since contributed to our knowledge of this tissue (for references, see Nilsson 1962[1 2]) The view obtained of the normal ultra structure of the uterine epithelium afforded a basis for studies on the ultrastructure of the pathological conditions in this epithelium Thus the appearance of hyperplastic endometrium (Wessel 1961) and of adenocarcinoma (Sirtori 1960 Sirtori and Morano 1961 Nilsson 1962) was described The present paper demonstrates some of the ultrastructural differences which are present between normal and cancerous uterine epithelium

Material and Methods

The specimens of the normal endometrium were obtained with a biopsy curette from 9 women in the follicular phase and from 8 women in the luteal phase This material and the methods are described and discussed in earlier papers (Nilsson 1962[1-])

The specimens of the cancerous endometrium were obtained with a biopsy curette from 1 woman in the late secretory phase and from 3 women in the menopause This material and the methods are described and discussed in an earlier paper (Nilsson 1962)

Results

The Cell Surface The normal uterine epithelium possessed apical long microvilli during the follicular phase and irregular projections during the luteal phase of the ovarian cycle The lateral cell surface of adjacent cells showed terminal bars and desmosomes The basal cell surface was slightly irregular, and the basement membrane separated the epithelial cells from the cells of the connective tissue (Fig 1)

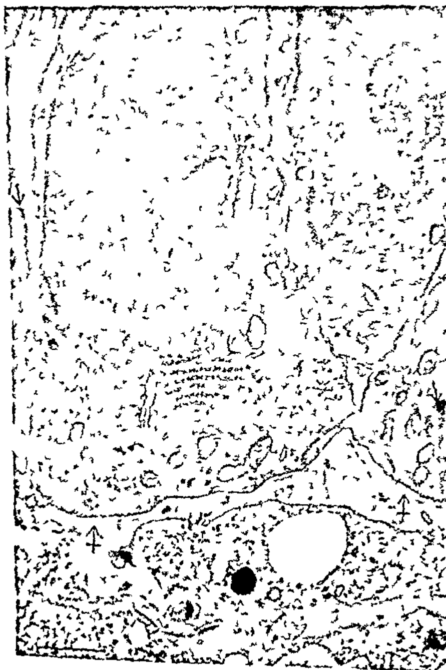
The cancer cells showed a luminal surface, which either possessed microvilli or were irregular (Figs 2–4) As the outline of the cancer cells differed even in the same specimen, the appearance of the cell surface was not as consistent as in the normal uterine epithelium Terminal bars and desmosomes occurred in about the same number as in the normal cells The basal cell surface was slightly irregular with the exception of its appearance in the low squamous type of cancer cell (Fig 3) In these cells, the cell membrane had projections with a length of several microns into the connective tissue The basement membrane followed the outline of the basal cell surface of most cancer cells However, rows of cancer cells were observed, where the basement membrane was lacking (Fig 2)

The RNP-particles, the α-Cytomembranes, and the Type A and B Cells The epithelial cells of normal endometrium in the follicular phase contained a rather high amount of free ribonucleo protein (RNP) particles and α cytomembranes Also during the luteal phase, these cell components were commonly noticed

The cancer cells contained a varying amount of RNP-particles and α-cytomembranes According to Caspersson and Santesson (1942), those cells that were rich in these components were named type A cells and the other cells named type B cells In addition to the high amount of RNP particles and α-cytomem

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Fig 1 Basal part of human uterine epithelium at the early luteal phase of the ovarian cycle *Two nuclei of epithelial cells are visible in the upper half* of the picture Mitochondria and small RNP particles are observed in the cytoplasm The adjacent lateral cell surfaces show desmosomes ( ) The basement membrane (←→) follows the outline of the basal cell surface Parts of connective tissue cells are seen under the basement membrane × 19 000



branes, the A cells also demonstrated a rather dense ground substance These properties rendered the A cells recognizable in the electron micrographs (Fig 2)

The Mitochondria The epithelial cells of normal endometrium in the follicular phase contained mitochondria, which had a maximum length of about 0 5 μ and a width of about 0 2 μ During the luteal phase, mitochondria with a changed shape and size appeared Some mitochondria grew in length to about 4 μ, but their width remained at about 0 2 μ Some other mitochondria attained a spherical shape with a diameter of about 2 μ These mitochondria contained many internal cristæ

The cancer cells demonstrated a varying number of mitochondria Some cells were filled with mitochondria, whilst others contained very few The cells which showed few mitochondria mostly were poor in the number of α cytomembranes The shapes of the mitochondria were varying, and similar types of mitochondria as noticed in the normal epithelium were observed in the adenocarcinoma cells However, the large, spherical mitochondria of the cancer cells contained only a few, irregular cristæ This type of mitochondria was rather common in those cancer cells which only showed a few mitochondria

The Inclusions The epithelial cells of normal endometrium demonstrated several types of inclusion as lipid globules, granulated bodies, and glycogen rich secretion The lipid globules, which were observed as dark, irregular structures of varying size, occurred sparsely in both the follicular and luteal phase of the ovarian cycle The granulated bodies had a diameter of 0 2–1 μ and contained small granules of varying size and electron density The granulated bodies seemed to be most frequent during the late follicular phase but were present also during the other stages of the ovarian cycle The glycogen rich secretion was observed as lightly staining zones of varying size These zones had an amorphous or slightly granulated appearance

Fig 2 A row of adenocarcinoma cells is observed in the upper part of the picture blood cells or connective tissue cells are noticed in the lower part of the picture The epithelial cells are lacking the basement membrane An A cell with a comparatively high electron density of the cytoplasm is observed to the left in the epithelial membrane × 4 000


2μ
2

The cancer cells contained a varying amount of inclusions For instance, some cells were loaded with lipid globules (Fig 4), whilst others contained only few of them The granulated bodies and the glycogen rich secretion of the normal epithelium were seldom noticed However, a type of granule was frequently ob served in some cancer cells These granules had a maximum size of about 0 5 μ The interior of the granules was composed of a dense substance with a varying amount of vesicles, membranes, and dark irregular areas (Fig 5)

Discussion

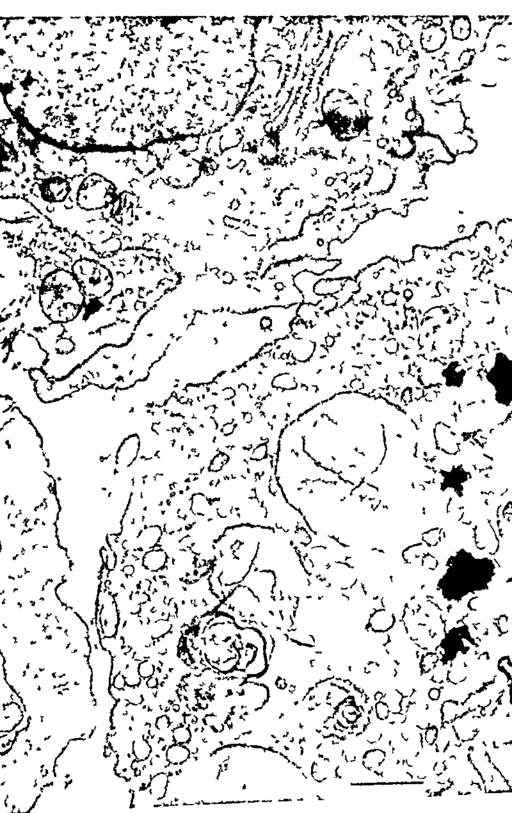
The cells of uterine adenocarcinoma are known by light micro scopy to differ in morphology This difference is due to the different degrees of anaplasia and degeneration in the cells Anaplasia implies change into a less differentiated and often more quickly growing form of cell It is observed, among other changes, as a decrease in number of cytoplasmic components (Oberling and Bernhard 1961) Degeneration implies, among other things, a decrease in the activity of the cell and is caused by different fac tors as aging, insufficient oxygenization, and toxic influences The morphology of the degenerating cell is varying, and a decrease or an increase of different cell organelles and inclusions occurs It is therefore logical that the present microscopical study demonstrated a varying number and structure of the cellular components in the adenocarcinomas But it is difficult to classify the different mor phological changes as depending upon anaplasia or degeneration However, some conclusions can be drawn on the cause of some of the observed changes

The luminal cell membrane of the normal uterine epithelium has an appearance which varies during the ovarian cycle, but all the cell surfaces of a certain specimen are rather similar in structure It seems that the structure of the cell membrane is correlated to the function of the cell (Nilsson 1962[4]) The luminal surface

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Fig 3 Low squamous type of adenocarcinoma cells The mitochondria are vacuolized, which might be a sign of *post mortem* changes at the fixation The basal cell surface shows several long projections into the connective tissue × 17 000





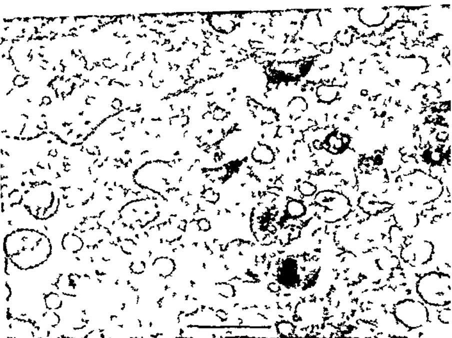


Fig. 5 Part of adenocarcinoma cells. Cell membranes are seen in the upper left corner of the picture and parts of a nucleus in the lower left corner of the picture. Mitochondria and vesicles are observed in the cytoplasm. Several granules with a varying amount of vesicles, membranes and dark areas are present in the right half of the picture × 2 000

of the cancer cells however varies in structure in the same specimen. This probably reflects a difference in functional states of these cancer cells. However no correlation of the structure of the luminal cell surface to the functional state of the cancer cell is as yet possible.

The surface movements of many normal cells growing in tissue culture are mostly inhibited by contact with adjacent cells. This property is called contact inhibition (Abercrombie and Heaysman 1954). Some cancer cells however show a reduced

Fig. 4 Parts of some adenocarcinoma cells growing in a globe-like cell group. The cell surface has an irregular outline. The cytoplasm contains different types of inclusions as dense granules, vesicles and lipid globules × 16 000

degree of contact inhibition This has been suggested as one reason for the invasive power of cancer cells (Ambrose 1958) In the present electronmicrographs, the basal surface of some low adeno carcinoma cells possessed long projections into the connective tissue This might be a sign of a reduced degree of contact inhibition and of an increased capacity to invasiveness of these cells

Caspersson and Santesson (1942) described in some adenocarcinoma the presence of cells with a high content of nucleic acids The authors named these cells type A cells The present investigation shows that cells with these characteristics also are present in the carcinoma of the uterine corpus The significance of the rather dense ground substance in the A cells is not yet known It might, however, be a sign of another form of cytoplasmic nucleoprotein than that visualized in the α cytomembranes and RNP-particles

The inclusions in the form of lipid globules were numerous in some adenocarcinoma cells Although the number of the lipid globules in the normal uterine epithelium varies during the menstrual cycle (Aschheim 1915, Black, Heyns and Gillman 1941), no normal cells have as yet been observed to contain so many lipid globules as do some cancer cells As the appearance of lipid globules in a cell is commonly a sign of degeneration, the lipid-rich cells of the present investigation are probably degenerating

The granules with the varying amount of vesicles, membranes, and dark areas, observed in some cancer cells, were sometimes similar in structure to ingested bacteria (Gezelius 1961) But some granules had also similarities with the granulated bodies of the normal uterine epithelium These bodies were suggested to be lysosomes (Nilsson 1962), which are cell organelles rich in different hydrolysing enzymes (de Duve 1959) The presence of several lysosomes in some cancer cells is in accordance with an assumption by de Duve (1961) He suggested that the destructive effect of the cancer cells on the surrounding cells might be a result of a high number of lysosomes These should furnish hydrolysing enzymes necessary for the destruction of the surrounding cells Another task of the lysosomes seems to be a participation in the turn over of lipid globules (Nilsson 1962[5]) Therefore, the

high number of lysosome like granules in some cancer cells might imply that these cells are synthesising or decomposing lipid globules at a high rate That state of a cancer cell might precede, among others, a degeneration with an accumulation of lipids in the cytoplasm However it is not yet known what is the significance of this type of granules in some of the cancer cells

The present investigation thus demonstrated a varying morphology of the cancer cell on the ultrastructural level As the cause of these changes is both anaplasia and degeneration, the morphological study of adenocarcinoma might give more information if the degenerative changes could be avoided A material that offers this possibility is the vaginal metastases from cancer in the body of the uterus If these are small the nutrition of the cancer cells should be sufficiently good to warrant a minimal degree of degeneration A further advantage of this tissue is that there is no risk of intermingling in the tissue of non malignant uterine epithelial cells An electron microscopical study of these vaginal metastases is in progress

SUMMARY

The appearance of the cell surface in the normal uterine epithelial cells varied regularly during the menstrual cycle but that of the surface in the adenocarcinoma cells was inconsistent in the same specimen This might imply a difference in functional states of these cancer cells Some squamous cancer cells showed deep projection into the connective tissue This was interpreted as a sign of reduced contact inhibition of these cancer cells The type A cells of the uterine adenocarcinoma demonstrated a dense cytoplasm with many free or membrane attached RNP particles It was suggested that these properties reflected the high amount of nucleoprotein in the A cells The ultrastructure of the mitochondria was varying probably depending upon the degree of anaplasia or degeneration in the cancer cells This was also assumed to be the cause of the variation in number and structure of the different types of inclusions in the cancer cells

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Acknowledgement

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From the Department of Gynæcology (O Koller, M D) The Norwegian Radium Hospital, Oslo Norway

ADENOCARCINOMA CERVICIS UTERI

A Clinical Study

BY

PER BERGSJØ

Adenocarcinoma of the uterine cervix generally constitutes about five per cent of all cervical carcinomas Thus in two German series, the figures were 4 5 and 3 per cent respectively (Drescher, 1949, Limburg and Thomsen, 1949) The most important question concerning this condition has been whether radiotherapy or surgery should be the primary treatment. The answers to this have of necessity, been based on fairly small series In the beginning of the radiotherapeutic era many experts considered the cervical adenocarcinomas highly radioresistant. Then, in 1935, Nilsson published the results of treatment of 80 cases from Radiumhemmet, Stockholm He found that a few cases were radioresistant, but his conclusion was that radiotherapy should be used, except possibly in some exophytic growths where surgery may be preferable The 5 year survival was about the same as for squamous cell carcinomas yet the prognosis was considered somewhat more unfavourable as a higher percentage of the adenocarcinomas were in the early stages at the time of diagnosis Kottmeier (1953) reported a 54 per cent apparent recovery rate in the stage I and II cases of cervical adenocarcinoma treated by radiotherapy, which was no worse than the corresponding rate in patients with squamous cell carcinomas Kottmeier suggests that radioresistant cases are highly malignant tumours in which any sort of treatment is bound to

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fail Drescher (1949) also concluded that the usual treatment must be a combination of radium and roentgen rays In early cases surgery may be performed after primary roentgen irradiation His series consisted of 79 cases with a 5-year recovery of 24 per cent, as compared to 29 per cent for the total group of cervical carcinomas Limburg and Thomsen (1949) performed surgery in selected early cases They report 53 6 per cent and 25 0 per cent 5-year recoveries in stage I and II adenocarcinomas respectively, whereas the corresponding figures in squamous cell carcinomas were 77 7 and 56 0 per cent Gusberg and Corscaden (1951) *found 7 radioresistant tumours in a group of 38* cervical adenocarcinomas, while 22 responded to radiation

Material

During the years 1945 to 1960 inclusive, 169 patients were treated in the Norwegian Radium Hospital for adenocarcinoma *of the uterine cervix Classification has been made according to* the rules of the 'Annual report on the results of treatment in carcinoma of the uterus , and care has been taken to omit cases of "carcinoma corporis et endocervicis' and stage o' cases Fourteen cases of adenoacanthoma are included in the material, but no further attempt at histological subgrouping has been made

The group comprises 4 1 per cent of the total number of *cervical carcinomas admitted during the same period* The present study is an analysis of these 169 patients with cervical adenocarcinoma, and an attempt to compare the findings with available data on patients with squamous cell carcinomas of the cervix

Presentation of data

Eight patients of the 169 (4 7 per cent) had a stump carcinoma One of the patients had an ectopic urinary bladder and a mal formation of the vagina

In Fig 1 the age distribution is compared with that of all cervical carcinomas in Norway 1953—1954 The latter group includes 7 5 per cent of stage o' cases In the adenocarcinoma group there was a peak in the 35—39 years age group, followed

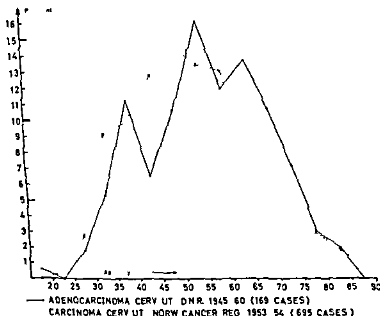


Fig 1 DNR The Norwegian Radium Hospital
Norw Cancer Reg The Cancer Registry of Norway

by a drop in the next 5 year age group The youngest patient was 17 years old The mean age was 53 7 years, compared with 48 8 years for all cervical carcinomas treated at the Norwegian Radium Hospital from 1932 to 1955 adjusted for stage incidence The latter point supports the impression given by the age distribution curve that the adenocarcinomas generally appear a little later in life than the squamous cell carcinomas

The ratio married patients/single patients was 4 45, compared with 6 25 in a total of 2 756 carcinoma cervicis uteri patients from Sweden (Kottmeier 1953) The percentages of nulliparæ in the same two materials were 13 2 and 8 7 respectively The mean number of births per patient in the adenocarcinoma group was 2 2

The clinical stages are shown in Table I In a corresponding overall series of carcinoma cervicis uteri there is a greater proportion of advanced cases

Table I *Clinical Stages — 169 Patients*

Stage I	72 patients	42 6 per cent
„ II	51 ,	30 2 „ „
„ III	34 ,	20 1 „ „
, IV	12 „	7 1 „ ,

Table II *Primary Treatment — 169 Patients*

Radiation only	122 pat
Radiation followed by radical hysterectomy and deep pelvic lymphadenectomy	5 ,
Radiation followed by simple hysterectomy and deep pelvic lymphadenectomy	2
Radiation followed by simple hysteroctomy	20 ,
Radiation followed by removal of the cervical stump	2 ,
Simple hysterectomy only	3 ,
Simple hysterectomy followed by radiation	11 ,
Radical hysterectomy and deep pelvic lymphadenectomy followed by radiation	1 ,
Removal of the cervical stump followed by radiation	1 ,
No treatment, and inadequate treatment	2

The treatment is outlined in Table II The modes of treatment changed slightly during the period covered by this study In general, however, the principles have been primary radium treatment by a modified Paris technique, followed by simple or radical hysterectomy in early cases and by external radiation in advanced cases For various reasons exceptions to this rule were common in this series One patient refused treatment, and in one insane patient treatment could not be carried out The three patients treated primarily by operation only were later given radiation because of recurrences, and two treated radiologically were later operated upon for the same reason

At least 16 (10 per cent) of the adenocarcinomas must be classified as radioresistant as biopsy a few months after full treatment revealed persisting cancer Seven of these were in stage I, eight in stage II and one in stage III

Five—and ten year results are presented in Table III Table IV shows a direct prognostic comparison between adenocarcinomas and squamous cell carcinomas treated at the Norwegian Radium Hospital between 1945 and 1956 The prognosis for the cervical

Table III 5 *and 10-Year Survivals Treated Patients*

	Stage	No of Patients	Died of Cancer	Died — Other Causes	Alive with Evidence of Disease	Alive no Evidence of Disease
Observation	I	44	16	1	4	23
time	II	36	21	0	2	13
5 years	III	25	19	0	1	5
	IV	8	8	0	0	0
	Total	113	64	1	7	41
Observation	I	24	14	0	0	10
time	II	20	13	0	1	6
10 years	III	10	9	0	0	1
	IV	4	4	0	0	0
	Total	58	40	0	1	17

Relative apparent 5 year recovery rate all stages 36 3 per cent
Relative apparent 10-year recovery rate all stages 29 3 per cent

Table IV *Comparison between the 5 Year Results of Treatment of Adenocarcinomas and Squamous Cell Carcinomas The Norwegian Radium Hospital 1945—1956*

Stage	Adenocarcinoma			Squamous Cell Carcinoma			Statistical Evaluation		
	No of Patients Treated	Alive and Symptomfree		No of Patients Treated	Alive and Symptomfree		χ^2	Degrees of Freedom	P
		No	Per cent		No	Per cent			
I	44	23	52 3 %	704	514	73 0 %	9 3	1	P < 0 01
II	36	13	36 1 %	969	509	52 5 %	4 0	1	0 02 < P < 0 05
III	25	5	20 0 %	713	201	28 2 %	0 8	1	0 3 < P < 0 5
IV	8	0	0 %	160	9	5 6 %	0	1	P = 1
Sum χ^2							14 1	4	P < 0 01
Total	113	41	36 3 %	2546	1233	48 4 %	7 0	1	P < 0 01

adenocarcinomas is significantly worse than for squamous cell carcinomas This is mainly due to the differences observed in stage I and to a lesser degree, in stage II

Fig 2 and Table V show the survival rates in the whole group of treated patients The steep decrease in survivals covers the first four years after which the curve flattens

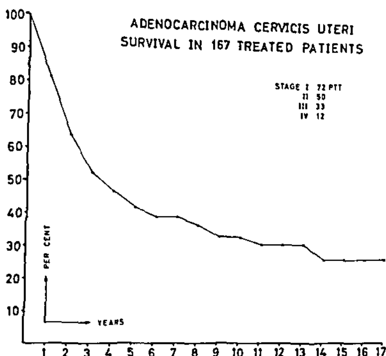


Fig 2

Discussion

The ratio adenocarcinoma/carcinoma cervicis uteri seems to be fairly constant in populations with similar racial, cultural and religious background, as exemplified by the above-mentioned German series, and by the present one On the other hand, Gusberg and Corscaden (1951) stated that the majority of their cases of cervix cancer in Jewish women were adenocarcinomas These, as well as the observations on age distribution, marriage rates and parity favour the idea that the adenocarcinomas are less dependent on external factors than are the squamous cell carcinomas They seem to be related to a 'corpus rather than a "cervix factor

The observed decrease in morbidity between the ages of 40—44 was first thought to be due to chance However, on studying Drescher's (1949) paper, I was surprised to find a curve almost identical to the present, particularly in regard to the dip

Table V *Survival in 167 Treated Patients with Adenocarcinoma Cervicis Uteri*

Time after Treatment in Years	Number of Patients			$o_t - \frac{w_t}{2}$	$\frac{d_t}{o_t - \frac{w_t}{2}}$	$1 - q_t$	Survival Rate $p_t\ P_{(t-1)}$ $P_{(t-2)}$
	Alive at Beginning of Interval	Observ Time too Short at Interval	Dead during Interval				
(t)	(o_t)	(w_t)	(d_t)		(q_t)	(p_t)	(P_t)
0	167	0	0	167	0 000	1 000	1 000
1	167	0	31	167	0 186	0 814	0 814
2	136	11	28	130 5	0 215	0 785	0 638
3	97	2	17	96	0 177	0 823	0 525
4	78	10	8	73	0 110	0 890	0 467
5	60	6	6	57	0 105	0 895	0 418
6	48	5	3	45 5	0 066	0 934	0 391
7	40	4	0	38	0 000	1 000	0 391
8	36	5	2	33 5	0 060	0 940	0 367
9	-9	3	3	27 5	0 109	0 891	0 327
10	-3	5	0	20 5	0 000	1 000	0 3-7
11	18	4	1	16	0 063	0 937	0 306
12	13	1	0	12 5	0 000	1 000	0 306
13	12	4	0	10	0 000	1 000	0 306
14	8	2	1	7	0 143	0 857	0.262
15	5	3	0	3 5	0 000	1 000	0 262
16	-	1	0	1 5	0 000	1 000	0 262
17	1	1	0	0 5	0 000	1 000	0 262

between 41 and 45 years of age These two parallel observations point to a possible biological significance

The distribution of the clinical stages in the adenocarcinoma group, with more early cases than in the total group of cervical carcinomas contrasts the poorer prognosis observed in these patients It seems likely that the adenocarcinomas have a greater tendency to early metastases a point also made by N i l s s o n (1935) It is also possible that the staging of the adenocarcinomas is not strictly comparable to that of the squamous cell carcinomas, because of biological differences which may be reflected in the clinical evaluation

Regarding the therapy, there is no justification for changing

our above-mentioned principles of treatment We must only hope for as few exceptions from the rule as possible, in order to get a true evaluation of our therapeutic efforts

SUMMARY

The 169 patients treated for adenocarcinoma of the uterine cervix at the Norwegian Radium Hospital from 1945 to 1960, are reviewed The age distribution and the mean age of the group show that the adenocarcinomas appear a little later in life than do the squamous cell carcinomas of the cervix A peak in the age distribution of the adenocarcinoma patients between 35 and 39 years of age, followed by a drop in the next 5-year group, may be of biological significance

The distribution of clinical stages shows more cases with early lesions in the adenocarcinoma group than in the corresponding overall group of cervical carcinomas However, by direct comparison the 5-year survival is significantly worse in the former group

The principles of treatment have been primary radium treatment by a modified Paris technique, followed by simple or radical hysterectomy in early cases and external radiation in advanced cases The relative apparent recovery rate for 113 patients observed during 5 years is 36 3 per cent, and for 58 patients observed during 10 years 29 3 per cent

The steep decrease in survivals covers the first four to five years after treatment

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EIGHT YEARS' EXPERIENCE OF X-RAY MOVING BEAM THERAPY OF CERVICAL CARCINOMA

BY

C E UNNÉRUS AND P KARSTILA

Gynæcological cancer has for decades been in a special position in medicine, partly because it responds to both operative treatment and radiotherapy, but partly also on account of the number of special difficulties that treatment has always involved

The treatment can also be divided, after Corscaden (1951), into preventive, curative and palliative when preventive refers to, say, skilful management to keep trauma minimal, e g making use of the opportunities for a Cæsarean section at the correct time and in otherwise uncertain cases The result is fewer traumata and the resultant chronic irritative conditions erosions, etc Another aspect of prophylaxis is regular medical examinations and the treatment in time of minor affections

The gynæcological forms of cancer account in many countries on an average for close on 1/3 of the total incidence of cancer

The anatomical conditions in the female pelvis always involve a special factor of difficulty for treatment, whether operative or radiotherapeutic

In most countries operative therapy is considered in cases of Grade 0 and I, but in some countries there is a tendency to manage certain Grade II cases operatively

In deciding whether the treatment of choice is operation or radiation it is necessary first to find out whether the diagnostic facilities admit of a sufficiently reliable classification As long as cervical carcinoma is classified on the ba is of fairly simple clinical

methods a considerable number of cases will be overlooked in which the spread via the lymphatic channels for example is more advanced than was assumed Hence many operations result in damage to tissue which is already affected by cancer

When samples are taken from fairly remote lymph nodes a possibility that must always be borne in mind is that the section itself perhaps does not coincide with the right layer It is just these facts that in our opinion are the vital *points in comparing* statistical data from different sources They are important also because, international precepts notwithstanding, diagnostic evaluation always has certain local colouring, as have operative methods, etc

Attention was called by Heyman (1944) to the difficulty of correct classification " In spite of the fact that I have a personal knowledge of almost every individual case, I encountered great difficulty in classifying recurrences There was in fact a *constant feeling that the classification in at least half of the cases* was artificial, and I arrived at the conclusion that an exact classification of the recurrences is a rather hopeless task " He claimed moreover that it was by no means unusual to establish affected lymph nodes fairly far from the cervix This is distinct evidence that the case has in fact been inoperable or that operation is really contraindicated

Analysis of the experience gained *in different parts of the world* shows readily that radiotherapeutic clinics use radiotherapy alone, whereas gynæcological and other clinics where operative therapy is also practised have a fairly comprehensive choice of operations for cancer of the cervix The predominant ones are Wertheim and Schauta operations with minor local variants in the different clinics Furthermore, it is now fairly common for some clinics to combine radiation and surgical therapy

The Women's Clinics in Helsinki come in this last category The *series derives* from practically the whole country and is less easy to classify than the average series – as a large number of difficult cases are referred This can be assumed from the character of the hospital alone it is a teaching clinic for gynæcologists The evaluation of the treatment of the cases must perhaps be viewed to some etxent also against this *background, the technique of*

cancer surgery must be taught at the same time as instruction is given in modern cancer diagnosis

However, it has been possible in spite of the size of the hospital – over 400 beds – to maintain a satisfactory uniformity in the schemes of treatment followed in both clinics of the hospital The indications for surgery were established in much the same way, with the limit drawn at Grade II, in some cases a number of Grade I cases were not operated on

The operative indications could perhaps have been established more strictly in a number of cases from the radiotherapeutic standpoint.

There has been a certain diversity in radiation therapy itself in the last few years, because radium applications have been per formed by different persons and, – of necessity because of inade quate apparatus

Methods and Material

To establish the best possible basis of comparison we collated the results which were obtained through the combination of intra cavitary radium or radioactive cobalt Co^{60}) plus rotatory irradiation (pendulum convergence therapy) For this, a Muller pendulum therapy unit obtained in 1953 was used

The first year of its use, 1954, meant groping after methods and experience as the apparatus was the first of its kind in Europe, at any rate the first in the Nordic Countries

We have now collected a series of patients who were given only this type of radiotherapy in addition to intracavitary radium and/or cobalt treatment Although we had access to the body-cavity tube introduced by Martius, it was not used for supplementary therapy because of some uncertainty as to whether the site of application was exactly right Pendulum convergence therapy appears to be strongly indicated for cancers of the cervix of Grades II-IV on account of the advantageous localisation of the radiation tube against the parametria The series thus com prises all grades of cervical carcinoma

The apparatus has been in full operation daily Unfortunately, the only way in which is has been possible to "accomodate all

the patients is by treating some with the less beneficial old fashioned method of a fixed field There was no actual selection, a patient was placed under *pendulum-convergence therapy as* soon as there was a vacancy In this way there originated a non selected control series

The series includes only cervical cancers of Grades I–IV since grade o would not, of course, have justified rœntgen therapy of this type The fact that this therapy was used for grade I was because we considered it preferable to forestall the possibility of *a spread rather than disregard a possible invasion in the regional* lymphatic channels

Therapeutic data The field measured 3 5×7 cm, 200 kV, the pendulum angle was 200 deg , the translation angle ±30 deg The pendulum movement was over both sides with a lead shield above the hip joints, the field displaced 4 5 cm laterally from the median line Each individual treatment lasted 18 min , *i e* a deep dose of 200 r We have endeavoured to an increasing extent to achieve an isodose control of radiation in the true pelvis and calculated the average dose of the 3 intra cavitary applications in terms of r and not of mgeh* as was previously customary To this were added the doses of pendulum convergence radiation, thus the parametria received an average deep dose of 4,500 r As it is only in the last year that physicists have been employed at the hospital it is possible that the dose measurements have perhaps not always been absolutely accurate owing to shortage of time and material, etc This applies especially to the first years

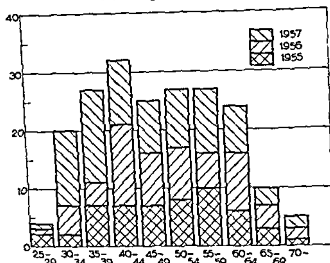
The number of cases managed by X-ray moving beam therapy totalled 1,171 by March 1,1962, but only 893 of them were so to say true cases, *i e* patients who had received only pendulum-convergence therapy as percutaneous irradiation

There was still too little experience in the first few years and relatively few accounts in the literature of direct clinical results Hence the series from those times was still fairly small The number of "true" cases has subsequently increased steadily There is now a 5 year observation period for 250 cases Only cases of grades I–IV are included

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* mgeh=milligram equivalent hours

Table I *Age Distribution*



It may perhaps be mentioned in this connection that we have also irradiated a number of other cases of gynæcological cancer with the rotatory irradiation method, in particular cases of ovarian cancer

In the cases in which 'true pendulum convergence therapy was not possible, different combinations with fixed field, radiotherapy, chemotherapy, etc were used The scheme permitted as individual treatment as possible, but as the series is extremely heterogeneous it does not lend itself to comparative analysis The result of pendulum convergence therapy can, then, be compared only with the results of the total of the cases with cervical carcinoma

Results

The present series is first analysed from different standpoints *Table I* shows the age distribution of the patients in all the grades

The peak coincides with the 40–45 year group and the collum is surprisingly high even in the group aged 30 and over Only when cases aged 65 or more are considered does the collum shrink It must however be considered here that the number of

Table II. Anamnesis and Grade

Symptom	Grade I	II	III	IV
Duration				
– 1 month	2	8	4	-
1– 3 months	8	17	12	-
3– 6 „	14	41	10	-
6–12 „	6	31	13	1
1 year–	3	11	2	-
No information	7	8	2	1
Total examined	40	116	43	2
Type				
Leukorrhea	14	30	10	-
Hæmorrhages	28	98	38	1
Pain	10	45	22	-
Other symptoms	6	23	11	-
Bladder complaints	2	4	3	-
Rectal „	1	1	2	-
No information	7	7	2	1

In the 201 first cases of the material the occurrence of symptoms are shown in the different grades of cervical carcinoma.

living women in this age group is considerably lower also in a normal population series. Three years, 1957, 1956 and 1955, were chosen to exemplify the age distribution.

Table II shows the occurrence of symptoms in the different grades of cervical carcinoma.

This material does not comprise all but only the first 201 cases analysed in this way. As regards the duration of the symptoms, it is striking that the duration was ½ year or shorter in such a great proportion of the cases. The material does not perhaps impart anything essentially new concerning the type of the symptoms. Leukorrhea and irregular episodes of bleeding are the domiant symptoms in all grades, pain appears most distinctly from Grade II on.

Before the final results are reviewed it may be of interest to consider the effect of the therapy on the status of the parametria

Table III *Changes in the Parametrial Status during Therapy*

After Therapy	Before Therapy							
	Normal		Shrinkage		Thickening		Nodosity	
	No.	%	No	%	No	%	No	%
Normal	41	59	12	52	27	57	13	32
Shrinkage	10	14	3	13	6	12	8	19
Thickening	17	24	7	31	9	19	13	32
Nodosity	2	3	1	4	6	12	7	17
Total	70	100	23	100	48	100	41	100

This appears in Table III It can be seen distinctly that this form of therapy is beneficial in parametrial involvement

The changes in the blood picture in cervical carcinoma of the three lowest grades were also studied (Table IV) Grade IV was excluded on the grounds that these cases may already have had changes in the hæmatogenic organs or in any case a greater likelihood of genital toxic and other changes in status

Table IV *Changes in the Blood Picture*

	Grade		
	I	II	III
Hgb			
Elevated	60	59	55
Unchanged	16	13	12
Lowered	24	28	33
Erythrocytes			
Elevated	58	53	55
Unchanged	3	4	2
Lowered	39	43	43
Colour index			
Elevated	48	47	38
Unchanged	13	12	10
Lowered	39	41	52
Leukocytes			
Elevated	38	40	38
Unchanged	5	3	7
Lowered	57	57	55

Table V *Anamnesis and Mortality*

Symptom	Survivals	Deaths after			
		1 year	– years	3 years	4 years
Duration					
– 1 month	7	2	3	1	1
1– 3 months	15	10	8	4	–
3– 6 „	34	12	13	4	2
6–12 „	26	10	11	2	2
1 year–	11	1	3	–	–
No information	10	3	1	2	1
Total examined	103	38	39	13	6
Type					
Leukorrhea	30	6	9	6	1
Hæmorrhages	83	29	34	9	5
Pain	30	20	19	5	1
Other symptoms	12	10	12	4	1
Bladder complaints	5	4	1	1	–
Rectal complaints	1	–	3	–	–
No information	11	2	1	1	1

Correlation between the anamnestic data and mortality are shown

A marked improvement in hæmoglobin was established and the erythrocyte count was also elevated On the other hand, deteriorations typical of radiotherapy were established in the white blood picture All these patients received throughout the treatment hæmatinics, general medication to keep the blood picture in order In recent times Medica's Hepa-B- comp has been given to patients with more severe leukopenia It has proved to be an excellent preparation in this respect, as did Anabolin (Medica) later too

Table V shows the correlation between the anamnestic data and mortality It is not possible to draw any essential conclusions from it However, it may perhaps be interesting in later comparisons with the results of other therapeutic methods and longer observation periods

Table VI shows the correlation between the therapeutic results and the pathological diagnosis, which was studied in a partial series of 201 cases observed in detail for 5 years As was to be

Table VI *Survivals after Therapy and Pathological Diagnosis*

	Treated		Survivals after				
	Number		1 year	2 years	3 years	4 years	5 years
Ca epiderm	97	48	77	67	63	61	60
Ca anaplast	27	13	26	17	15	14	13
Ca spinocell	22	11	16	11	9	9	8
Ca keratin	16	8	10	5	4	4	4
Ca adenomat	11	6	9	8	6	6	6
Ca solidum	6	3	6	4	3	3	3
Ca papillomat	2	1	2	2	2	1	1
Ca planocell	1	½	1	1	1	-	-
No pathological diagnosis	19	9½	15	9	8	7	6
Total	201	100	163	124	111	105	101

In a partial series of 201 cases the correlation between the therapeutic results and the pathological diagnosis were studied for 5 years

expected, adenomatous cancer was established in only 6 per cent, and after 5 years there were still 6 symptom free survivors The diversity of the diagnosis arises from the fact that the cases were evaluated at times by different pathologists This applies to the earlier years Since 1956 the same pathologist has always evaluated the cases and the pathological flora will be more homogeneous in a later analysis

The total cervical carcinoma material of the Women s Clinics University of Helsinki, now shows a 5 year freedom from symptoms in a little over 50 per cent (a new analysis is being prepared) It must therefore be considered that the combination intra cavitary radium or radioactive cobalt + X ray moving beam therapy of the parametria produced an approximate 7 per cent increase in freedom from symptoms

However, judging by everything it is of the greatest importance that isodose thinking becomes common in the treatment of cancer this does not of course apply to radiologists only the mode of thinking for cancer therapy should be shared by all the clinics that are concerned with cancer This would make it easier to ensure that the tumour receives exactly the correct doses of

Table VII *Survival Rate after Therapy, Total Material*

Grade	Treated		Years Survived				
	Number	%	1 Year	2 Years	3 Years	4 Years	5 Years
I	54	21 6	51	49	47	45	44
II	142	56 8	117	98	89	82	78
III	51	20 4	35	28	25	23	20
IV	3	1 2	3	2	2	1	1
Total	250	100 0	206	177	163	151	143
%			82 4	70 8	65 2	60 4	57.2

radiation, so that no over-dosages occur with resultant 'hot spots" and tissue necroses, fistulas etc It will be possible, moreover, to apply radiotherapy to the actual metastasing pathways more correctly

Exact isodose curves are now drawn at the Women's Clinic for every treatment, every radiotherapeutic field is photographed to provide verification for localisation and dosage It is hoped, too, that it will gradually be possible to realise the plans for a radiation response study now and then in the course of treatment. For the

Table VIII

Group	Year	No of Cases	5 Years	4 Years	3 Years	2 Years	1 Year
A	1947	134	46 5 %	50	52	62 %	77
B	1952	94	53 %	57	60 5	68 %	80 7
	1953	146	41 5 %	44 5	49	52 5 %	67
	1954	127	52 %	52	57	65 %	83
A	1955	120	53 %	56	57	65 %	78
C	1956	113	–	59 5	62	70 %	84
	1957	138	–	–	–	79 %	90 5
	1958	148	–	–	–	74 %	85

The success of different radiotherapeutic methods in carcinoma colli uteri I-IV (survival rate in %)

A) modified Stockholm method (radium+rœntgen [Stehfeld])

B) Gottingen method (radium+rœntgen [intra vaginal+Stehfeld])

C) Tübingen method (radium and mobile radiation [Pendulum-convergence 250 kV])

According to H J Spechter, Tübingen (1961)

present this can be done only for some of the cases because of the shortage of experts

It is naturally very interesting to compare these results with similar analyses from elsewhere

There are still extremely few analyses of treatment with this apparatus Spechter (1958, 1961) made very useful observations on the working out of therapeutic methods and on experimental dose measurements His results thus have a special value He unfortunately moved from Giessen where he had started a comprehensive investigation series which he was then unable to supervise himself, to Tübingen where he began a similar series His analyses are tabulated below Group C corresponds most closely to our methods – the only essential difference is that Spechter used a 250 kV unit while the apparatus at the Women s Clinic is 200 kV

When this table was placed at our disposal Spechter (1961) did not have a 5 year follow up period but the results after 4 years show a great similarity to ours Minor deviations must always be expected perhaps owing to the differences in diagnosis of the different grades

Discussion

It may be interesting also to look back at really old statistics such as Heyman s (1944) data on the results at the Radiumhemmet in Stockholm during different periods of time The 5 year survival result for all 4 periods from the year 1914 to the year 1931 was 21 6 per cent, and for the period 1932–1938 33 1 per cent.

The cure percentage for all grades of cancer is generally around 40–50 for the pre- and post war years

The annual report of the Radiumhemmet for 1960 includes an analysis of the therapeutic results Freedom from symptoms after 5 years was achieved in 57 3 per cent in 1954 in 53 1 per cent in 1953 No cases of Grade 0 were included

There are few publications in Finland on the results achieved Kahanpää and Turtola (1955) published results of the treatment of cervical carcinoma at the Clinic of Radiotherapy, University of Helsinki, in 1942–1949, in fact quite a long time

Table VII *Survival Rate after Therapy, Total Material*

Grade	Treated		Years Survived				
	Number	%	1 Year	2 Years	3 Years	4 Years	5 Years
I	54	21.6	51	49	47	45	44
II	142	56.8	117	98	89	82	78
III	51	20.4	35	28	25	23	20
IV	3	1.2	3	2	2	1	1
Total	250	100.0	206	177	163	151	143
%			82.4	70.8	65.2	60.4	57.2

radiation, so that no over-dosages occur with resultant "hot spots" and tissue necroses, fistulas etc It will be possible, moreover, to apply radiotherapy to the actual metastasing pathways more correctly

Exact isodose curves are now drawn at the Women's Clinic for every treatment, every radiotherapeutic field is photographed to provide verification for localisation and dosage It is hoped, too, that it will gradually be possible to realise the plans for a radiation response study now and then in the course of treatment For the

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	1954	127	52 %	52	57	65 %	83
A	1955	120	53 %	56	57	65 %	78
C	1956	113	–	59.5	62	70 %	84
	1957	138	–	–	–	79 %	90.5
	1958	148	–	–	–	74 %	85

The success of different radiotherapeutic methods in carcinoma colli uteri I-IV (survival rate in %)

A) *modified Stockholm* method (radium+rœntgen [Stehfeld])

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C) *Tübingen* method (radium and mobile radiation [Pendulum-convergence 250 kV])

According to *H J Spechter*, Tübingen (1961)

High voltage therapy would certainly help to improve the results further But it can surely be taken for granted that cervical cancers and other cancers will still be treated in many parts of the world with these less potent sources of irradiation It is gratifying that good results can also be achieved with this method

Independent of all improved apparatuses and laboratory examinations, individual factors will surely come to play a dominant role in both the diagnosis and the treatment of cervical carcinoma These factors together with more effective educational work which will make patients seek medical advice in an earlier phase of the disease will have great significance for the further improvement of the cure percentage Effective team work between the various specialists must also be aimed at

SUMMARY

The results achieved in cervical carcinoma by a 'true combined therapy – intra-cavitary radium or radioactive cobalt plus percutaneous radiotherapy by the X ray moving beam method with a Muller apparatus – are analysed The improvement of the results was striking compared with earlier results from Finland and also in comparison with results achieved in other parts of the world

Careful isodose planning is of the greatest importance for good results Other conditions are a physicist to assist in the work, and good co operation between the clinics of the hospital In addition the cases must be considered individually 57 2 per cent freedom from symptoms after 5 years would not seem to be the final optimum achievable – there are indications of still further improvement.

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ago. The series consisted of 827 cases which were distributed as follows: Grade I=101, II=292, III=311 and IV=123. The number of "bad" cases was thus strikingly high at that time. Of the 767 cases treated, 43.8 per cent were free from symptoms after 5 years.

The present results show a distinct improvement. Since it can probably be assumed that intra-cavitary treatment has hardly changed, the improvement can be attributed at least to some extent to improved radiotherapy.

On the other hand, Fletcher (1959) and his co-workers reported in 1962 results of supervoltage therapy which showed that 5-year freedom from symptoms had risen in the total series of over 650 cases to 63 per cent (from the earlier 59 per cent prior to supervoltage therapy).

It is interesting to see here that the cure rate of adenocarcinoma has risen from 50 to 85 per cent. Fletcher's series is small, however, in both cases, 12 and 27, patients respectively.

It would naturally be possible to make further comparisons, but as the present series was collated specifically in an endeavour to bring out the possible benefit of X-ray moving beam therapy the comparisons have been restricted to these few.

Hence, it can be stated that there is only one prior major series of statistics available from Finland and that in comparison the present series shows a considerable improvement, 13.4 per cent. It is true that the antibiotics and other important drugs of the last decade must have contributed to the improvement of the general condition, but this alone cannot account for such a striking increase in the number of symptom-free cases.

It will be interesting to see analyses of the results of similar therapy from elsewhere, and comparisons between them and the results of different kinds of highvoltage therapy.

We hope to be able soon to publish another survey which will illustrate the coincident effect of certain chemotherapeutic agents.

It may be warranted, finally, to point out that we have a definite feeling that the improved calculation and placement of the radiation doses with the aid of isodose curves to which physicists have made valuable contributions will raise the standard of the results further.

Asanti Rita and Vesanto Tuulikki Acta obst. et gynec. scandinav 42 107 1963

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EFFECT OF THREATENED ABORTION ON FŒTAL PROGNOSIS

BY

RITA ASANTI AND TUULIKKI VESANTO

Fœtal organogenesis occurs during the second and third months of pregnancy At this stage disturbing environmental factors are known to give rise to fœtal malformation According to one opinion, different factors acting at a specific time produce anomalies that are similar or of a similar type, whereas identical environmental factors operating at some other phase of development induce anomalies of a different kind (Stockard, 1921) However, in the light of recent investigations the mechanism of production of fœtal malformations can hardly be accounted for by a single explanation The damage probably is the more severe the earlier the stage of fœtal development at which the teratogenic factor exerts its action (Knorr, 1960, Hohlbein, 1961)

One of the possible causes of fœtal malformation is deficient fœtal oxygenation (Mey, 1959, Ingalls, 1960, Hohlbein, 1961) which may result from partial separation of the placenta in cases of threatened abortion (Hollstein, 1958) The teratogenic effect of hypoxia has been demonstrated in numerous animal experiments (Ingalls *et al*, 1958) Interesting observations on the effects of hypoxia have been reported from Peru, where Alzamora and his co workers (1953) found that the incidence of cardiac anomalies was greater at high altitudes than in the coastal area Theoretically it might be considered that

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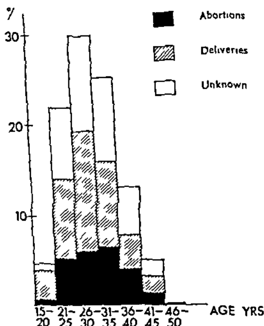


Fig 1 Distribution of cases by age and method of termination of pregnancy

abortion and premature labour in Departments I and II of Obstetrics and Gynæcology (Women s Clinics) of the Helsinki University Central Hospital during the 15 year period 1944–1958 The total number of patients was 1,299 Patients treated in the hospital s out patients department are not included

The data taken into consideration were the patient s age parity, possible previous abortions, previous children with congenital malformations infection, time of threatened abortion stated as lunar month of pregnancy nature and intensity of symptoms, and main features of the treatment given, especially with reference to hormone therapy The fate of the fœtus was followed as closely as possible and in some cases follow up inquiries were made by post

Of the 1 299 patients 527 (40 5 per cent) were found to have delivered at or near term and 296 pregnancies (22 8 per cent) terminated in abortion after discharge from the hospital No in-

premature uterine contractions alone – without separation of the placenta – may produce transitory hypoxia of the fœtus, since the placental blood vessels are compressed to some extent during uterine contractions It is also known that metabolic disturbances, even one of short duration, may have adverse effects if the fœtus is at the stage of organogenesis Since brain tissue is particularly sensitive to metabolic errors, especially hypoxia, it is likely that abnormalities will commonly occur in the central nervous system

It is, of course, difficult to differentiate hereditary defects from those induced by environmental factors It has been suggested that the ratio of lesions of environmental origin to those of genetic origin is 8 1 (Stahler, 1960) The majority of pregnancies in which the fœtus is severely malformed will terminate in abortion regardless of all therapeutic measures (Hollstein, 1958) According to Stevenson (1961), *c* 30 per cent of all zygotes are expelled dead, and about one-half of these are deformed Another credible concept is that threatened abortion and fœtal malformation have a common cause, and are not consequences of each other (Alkner *et al*, 1960) However, the mutual causality of these phenomena needs further investigation

Present Investigation

The object of the present investigation was to study the effect of disturbances in placental circulation in the light of the sensitivity of the fœtus to hypoxia at the organogenetic stage Since there are numerous sources of error in connection with the data obtained by retrospective inquiries in cases of fœtal malformation, we considered it preferable to carry out the study by systematic selection of all patients admitted to hospital because of imminent abortion during a period of 15 years The exclusion of patients examined in the out-patient department gave further assurance of the certainty of the diagnosis and effect of the treatment The study was not limited to the first months of gestation and includes, for proper elucidation of the situation, all patients with a diagnosis of threatened abortion, even if it is obvious that the cases in the last months of pregnancy includes threatening premature deliveries

The series consist of all patients hospitalized for threatening

Previous abortions were recorded in the case histories of 218 patients who delivered at or near term (41 per cent) In 41 of these cases the threatened abortion was associated with infection, whereas infection occurred in only two of the women who had no previous history of abortion In three patients with malformed children the abortion had been infected

Four parturients had previously delivered a malformed child All of them now had a normal child

About one half of the mothers who delivered at or near term had received progesterone treatment However, only one-third of the mothers whose pregnancy terminated in abortion had received progesterone No relationship was found between progesterone treatment and the nature of fœtal malformation

The results presented above were obtained from the case reports and the information on malformed fœtuses is based on the records of the maternity hospital In the early years the records were kept by midwives, whereas since 1954 a systematic examination of all children has been made by a pædiatrician

Follow up Study

Additionally a follow up study was made of all the parturients who had had threatened abortions during the second, third or fourth month of gestation There was a total of 296 children, and 277 of them had left the maternity hospital alive It was possible to follow the subsequent history of 39 of these children in the files of the Children s Clinic of the Helsinki University Central Hospital We sent a questionnaire concerning the condition of the child to the mothers of the remaining children Follow up information was obtained on a total of 54 per cent of the children on whom information was sought. A proportion of them were also brought for examination in the out patient department of the Children s Clinic As a result of this extended study we found 13 children with congenital defects

The malformations found in the 25 children in the primary series (Table I) and the 13 children in the follow up series are shown in Table II, listed according to the month of threatened abortion

formation was obtained on 476 patients (36 7 per cent) Fig 1 shows the distribution of the patients by age and the mode of termination of the pregnancy expressed as a percentage of each age group

The time of threatened abortion in each group of deliveries is seen in Table I

There was a total of 113 premature infants (20 7 per cent of all deliveries) Stillborn infants totalled 47 (8 6 per cent) There were 18 pairs of twins (3 1 per cent)

The patients were classified into five groups according to duration and intensity of the hæmorrhage in order to determine the relationship between these factors and the ultimate outcome of the pregnancies *The criteria of classification were as follows*

Group No	Criteria
0	Labour pains only, no bleeding
I	Bleeding on 1 day
II	Bleeding from 1 day to 1 week
III	Profuse bleeding during several weeks
IV	Bleeding during several months of pregnancy

The following Table shows the severity of the threatened abortion in the 25 cases of fœtal malformation

Group No	No of Malformed Children
0	4
I	9
II	11
III	–
IV	1[1]
	Total 25

The age distribution of the mothers of malformed fœtuses did not differ from that of the whole series

The distribution by parity of the total series and of the mothers of the malformed fœtuses was as follows

	I Para	II Para	III Para	IV Para	V Para	≧VI Para
Total series	37 8 %	32 0 %	17 4 %	7 4 %	1 9 %	3 5 %
Mothers of malformed fœtuses	58 2 %	25 0 %	8 4 %	4 2 %	4 2 %	-

1 Fœtus was hydrocephalic and was born in a state of maceration

Table II (Cont.)

Month of Threatened Abortion	Maternity Hospital Records	Follow-up Inquiry
V	Pes calcaneovalgus l dx Luxatio coxae cong l dx Digitus accessorius No I man. amb	
VI	Vitium cordis cong Defectus septi interventricularis Hæmangioma	
VII–X	Digitus pendulans m sin Nephrosis cong	

If we take into consideration the gestatory months important from the point of organogenesis (ab imminens mensium II and III) we obtain an incidence of 5.7 per cent of malformations in the maternity hospital series alone and of 11.4 per cent when the follow up series is included

Discussion

Concerning the outcome of the pregnancies it was observed that 22.8 per cent terminated in abortion However, the actual incidence of abortions was probably higher, since 36.7 per cent of the patients could not be followed up The pregnancy ended in delivery after X months gestation in at least 40.5 per cent of cases with a minimum of 545 potentially viable infants from 527 pregnancies This distribution conforms with those in most of the previous studies in the literature

The only significant finding in relation to age and parity was an unexpectedly high incidence of malformations in the children of primiparæ

According to the case histories, 4 per cent of the women who *delivered after* X months had previously had one or more abortions whereas there were only a few women with a diagnosis of habitual abortion The incidence of antenatal infection was 8.2

Table I *Distribution of Cases According to Time of Threatened Abortion and Condition of Fœtus on Delivery*

Month of Uterine Hæmorrhage	No. of Deliveries	Liveborn Fœtuses		Stillborn Fœtuses		Total Fœtuses	Malformed Fœtuses
		Full term	Premature	Full term	Premature		
II	82	67	13	1	4	85	7 (8 2 %)
III	120	106	12	1	6	125	5 (4 %)
IV	94	75	11	2	8	96	5 (5 2 %)
V	101	78	15	3	9	105	3 (2 9 %)
VI	63	40	15	–	9	64	3 (4 8 %)
VII–X	57	50	7	1	2	60	2 (3 3 %)
Not stated	10	8	1	–	1	10	– –
Total	527	424	74	8	39	545	25 (4 6 %)

Table II *Nature of Malformations in Delivered Children*

Month of Threatened Abortion	Maternity Hospital Records	Follow up Inquiry
II	Meningomyelocele	Ren duplex
	Hydrocephalus	Tetraplegia spastica
	Hydrocephalus incipiens + Digitus accessorius man amb	Hernia umbilicalis operata
	Pes equinovarus l a	Vitium cordis cong
	Pes equinovarus l a	Stenosis pylori
	Luxatio coxae cong l a	Retardatio mentis
	Hypospadia	Retardatio mentis
III	Vitium cordis cong	Vitium cordis cong
	Cor triloculare	(Stenosis art pulm + Defectus septi interatrialis)
	Fibroma cutis	Hernia umbilicalis operata
	Polypus ani	Spina bifida occulta vert S I
	Hæmangioma	Retardatio mentis
		Retardatio mentis
IV	Monstrum (forearms malformed and terminate in one digit)	Stenosis pylori
	Vitium cordis cong	
	Pes calcaneus l dx	
	Deformatio genu dx	
	Mongoloidismus (mother 41 yrs)	

tion (Stevenson, 1961) Thus a congenital malformation is not, as a concept, a clearly static condition

In the present series the incidence of malformed children according to the maternity hospitals records was 5 7 per cent, whereas the general incidence of malformations in the Women s Clinics of the University of Helsinki was c 2 per cent during the same period (Sjöstedt, 1962)

A *statistical analysis* (E Järvinen, M A, Institute of Occupational Health, Helsinki) was made of our series of cases The confidence limits were calculated by approximation based on Poisson s distribution and the significance of the numerical difference was determined by the χ^2 test It was found that our incidences are significant when the normal values are less than 3 per cent, as is in the incidence of congenital malformations

An interesting observation is that inclusion of the data obtained by the follow up inquiry raised the incidence of malformations two fold (11 4 per cent) although the inquiry was successful in only 54 per cent of cases

SUMMARY

The prognosis in threatened abortion is related to the severity of the symptoms the incidence of delivery of normal children being progressively lower with increasing duration of the bleeding Furthermore, the possibility of giving birth to premature or stillborn children is clearly greater in these cases It may also be concluded that after bleeding in early pregnancy the incidence of malformed children is increased

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per cent in the group who delivered at term The threatened abortion had been infected in 12 per cent of cases where the infant was malformed

The incidence of premature births was rather high (20 7 per cent), as also has been observed in similar earlier investigations (Tosetti, 1960) The incidence of stillbirths was 8 6 per cent

Classified according to the severity of bleeding, the number of malformed children increased up to group II, while in groups III and IV the fœtus was no longer viable From those cases treated with progesterone there were only two infants with malformations, one case of meningo-myelocele and one case of hypospadias The former was associated with habitual abortion (with a low pregnandiol excretion) and in the latter case the mother had a uterus bicornis Progesterone cannot therefore be incriminated as a cause of fœtal malformation

A number of similar studies have been published earlier The most important is that of Hollstein in 1958, consisting of statistics collected from various publications and totalling 1,343 parturients The percentage of malformed fœtuses in his series was 2 3 per cent Mey (1959) published a similar study, obtaining a malformation incidence of 3 1 per cent It is to be noted that the above mentioned and similar studies are based on the maternity hospitals' diagnoses It is obvious that many malformations such as congenital heart defects, kidney diesase, and congenital dislocation of the hip escape diagnosis unless a pædiatrician performs a routine neonatal examination For this reason the older statistics, in which the general incidence of malformation was 1–2 per cent, should be taken with some reservation For example, McIntosh states that observation of children up to the age of two years gives a general incidence of 7 5 per cent The practice of performing an autopsy on all stillborn children, which has become a routine only during the past few years, will doubtless impart additional information

The question ultimately is whether all malformations should be regarded as congenital It is possible that tissues which already are fully differentiated may later undergo degeneration A disease that has its onset after birth may have as its underlying cause a microscopic prenatal trauma that later leads to tissue degenera

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ON THREATENED ABORTION

BY

H HANSEN L NILSSON AND L ZETTERGREN

In a previous paper one of us (Nilsson, 1962) reported on a series of women with threatened abortions treated with progesterone preparations, placebo and sedatives respectively Treatment with progesterone was not shown to give better result than that with either placebo or sedatives

Some of the figures given in that paper were preliminary since some patients in the series were still pregnant when the paper was published All the patients have now been delivered

In the present paper we shall at first briefly give the final figures concerning the effectiveness of treatment with progesterone or placebo Thereafter we shall discuss some other findings in our series of threatened abortions

As seen in the previous paper the series consisted of 253 cases of so-called threatened abortion

The material was divided into Series I and II

In Series I alternate patients received progesterone preparations and the other patients were given sedatives only

In Series II alternate patients received progesterone preparations and the others a placebo In this series the patients were not treated during the first day following admission since a 24 hour

Prolu on and proluton Depot (Schering)

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Table II *Gross and Microscopic Appearance of the Aborted Ova*

Group		All Abortions	Underdeveloped Fœtuses	Pathologic Ova	Regressive Changes	Uncertain	Normal Fœtuses	Abortion Not Inevitable
Series I	Progesterone	37	6	13	5	10	3	= 13
	Sedation only	31	8	7	7	5	4	= 9
Series II	Progesterone	24	2	6	3	10	3	= 13
	Placebo	31	5	10	7	6	3	= 9
Total		123	21	36	2[illegible]	31	13	= 44

decide in many cases whether the abortion was inevitable at the time of admission

Table II shows the appearances of the aborted ova Those cases where the fœtus was at most half as long as expected for the period of gestation are classified as underdeveloped fœtuses

The group pathologic ova comprises

1 Gros, anembryonic ova

2 Ova which on microscopic examination showed the appearance of a 'Zottenarmes Ei (Nilsson, 1957), (Fig 1)

3 Ova which on microscopic examination showed hydatidiform degeneration of the villi (Hertig and Edmonds, 1940, Nilsson 1957), (Fig 2)

In some cases where the abortion occurred soon after admission there were such marked regressive changes in the placenta that the ovum could not have been viable at the time of admission These changes were either fibrosis (Fig 3) or necrosis of the villi (Fig 4)

If abortion occurs more than a few days after admission one cannot decide whether or not the regressive changes occurred before or after admission In some cases regressive changes are absent or very slight and in other cases no egg or only decidua has been available In all these cases the time and cause of abortion are in doubt and consequently they are classified as uncertain

"Normal fœtuses" comprises those cases in which the fœtuses were normally developed for the period of gestation

sample of urine was collected for pregnanediol titration before progesterone was given.

In all except 4 cases of abortion, gross and microscopic examination of the conceptus was performed.

Effectiveness of treatment

In Table I the effectiveness of the treatment can be studied. As seen from the table about 40 per cent of the patients of Series I were delivered of viable children, whether they had received hormone treatment or sedatives only. *The difference in effectiveness between progesterone and sedation was not significant* ($x^2=0.48$).

Table I. *Outcome of Pregnancy*

	Group	Parturition	Abortion	Favourable Outcome per cent
Series I	Progesterone	22	37	37
	Sedation only	24	31	44
Series II	Progesterone	44*	24	65*
	Placebo	40**	31	56**
	Total	130***	123	51***

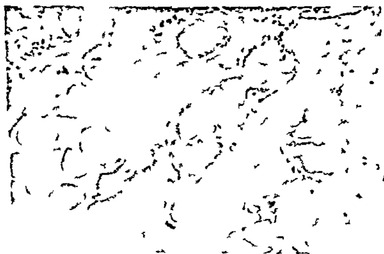
* 3 Premature labour, children died
** 2 Premature labour, children died
*** 5 Premature labour, children died

About 60 per cent of the patients of Series II were delivered of viable children whether they received hormone or placebo treatment. *The difference in effectiveness between progesterone and placebo was not significant* ($x^2=1.02$). *No definite beneficial effect of progesterone treatment has been established.*

However, not all the cases ending in abortion, were true threatened abortions at the time of admission. 'Threatened abortion' is a clinical term and applied to both established and unestablished cases. Only by gross and microscopic examination of the aborted ova in relation to the clinical data is it possible to



F g 3 F brotic chorionic vill of ovum aborted 12 weeks after cessation of menses Hæmotoxylin van G eson.



F g 4 Necrotic chorion c vill of ovum aborted 10 weeks after cessation of menses Hæmotoxyl n – van G eson

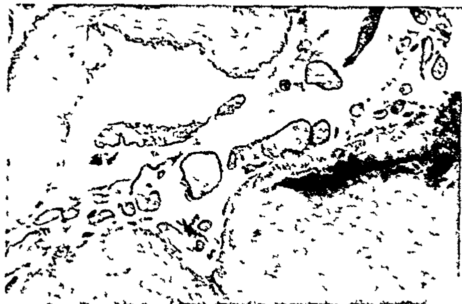


Fig 1 So-called zottenarmes Ei aborted 10 weeks after cessation of menses Note the short space between the chorionic membrane and the decidua. Hæmotoxylin – van Gieson



Fig 2 Chorionic villi of ovum aborted 11 weeks after cessation of menses Moderate hydatidiform degeneration is present Hæmotoxylin – van Gieson

Table IV *Time Elapsed from Admission to Abortion*

Group			1 day	4 days	1 week	weeks	3 weeks	4 weeks	>4 weeks	Unknown
Series I	Progesterone	Abortion not inevitable	1	3	4	3			1	1
		Abortion inevitable	3	14	4	2			1	
	Sedation	Abortion not inevitable		1	2	2			3	1
		Abortion inevitable	9	9	3				1	
Series II	Progesterone	Abortion not inevitable		4	2	3	1	1	1	1
		Abortion inevitable		5	3	1		1	1	
	Placebo	Abortion not inevitable		1	1	1	-		4	
		Abortion inevitable		15	1			1	4	1
Total			13	52	20	12	3	3	16	4

whether the fœtus had been passed without being observed or whether the ovum was anembryonic)

Tables I and III show a small difference in Favourable outcome between Series I and II This is partly due to the fact that the patients in Series II were not treated with progesterone or placebo until 24 hours had elapsed (N B abortions occurring during the first 24 hours have been excluded in Series II)

If only those cases where the abortion occurred late after admission are considered the differences concerning favourable outcome between the Series (I and II) even out

The pregnancy test used in the series was the Hogben test The accuracy of this test is not as high as desired but in Table V it is at least seen that the combination of a low output of pregnanediol and a negative Hogben test was associated with a bad outcome in all cases except one

At best the ova with normally developed fœtuses and the ova *with uncertain viability could be saved*, and therefore counted as truly threatened abortions retrospectively All other abortions have been counted as inevitable *We thus found that about 2/3 of the abortions in the series were inevitable at time of admission*

In Table III the effectiveness of the treatment has been cal culated after deduction of those cases of abortion which were subsequently classified as inevitable The results are expressed firstly as the percentage in which potentially viable infants were delivered and secondly as the percentage of cases in which the infants actually survived

Table III *Outcome of Pregnancy – Inevitable Abortions Deducted*

Group		Parturition	Abortion	Favourable Outcome per cent	Favourable* Outcome per cent
Series I	Progesterone	22	13	63	63
	Sedation only	24	9	73	73
Series II	Progesterone	44**	13	77	7-
	Placebo	40***	9	81	77
	Total	130****	44	75	72

* Dead children following premature labour deducted
** 3 Premature labour children died
*** 2 Premature labour, children died
**** 5 Premature labour children died

Table III shows that when the cases with inevitable abortions are excluded 2/3–3/4 of the patients in the series were delivered of living children *No difference in favour of progesterone treat ment is shown (Series I $x^2=0\ 76$ Series II $x^2=0\ 32$)*

Table IV shows the interval between admission and abortion If the ovum *is expelled soon after admission, it is very unlikely* that it was viable at the time of admission In fact on only three occasions did we find a fœtus of normal size in those cases where the abortion occurred within a week of admission (In many cases we did of course not find any fœtus at all It is impossible to say

tagens, can be discarded as a routine treatment of cases of so called threatened abortion

Habitual abortion

Habitual abortions were included only if they were also threatened Of the women in the series 79 were having their first abortion, 28 aborted for the second time and 13 were habitual aborters in the sense that they had had at least 3 consecutive abortions

The distribution in the series can be seen in Table VI

Placenta prævia

In the placebo group there were 2 cases of placenta prævia Both pregnancies were terminated by Cæsarean section In the first case, where bleeding first occurred in the 22nd week, the woman was later delivered of a living mature child In the second case, where bleeding first occurred in the 11th week the child died soon after delivery It is possible that the bleeding assumed to be a sign of threatened abortion in these cases was a sign of placenta prævia, but it cannot be excluded that other factors than the situation of the placenta could have been the cause of early bleeding Because of this we have not excluded these cases from the series In fact, the results are not influenced significantly whether or not these cases are included

Congenital malformations

An old question not yet satisfactorily answered, is whether or not patients who have bled during pregnancy are more likely to be delivered of malformed babies (Hudson *et al* 1945, Burge, 1951) Table VII shows the number and nature of malformations in the series

Hedberg *et al* (1962) in a prospective study on the causes of malformation found 61 malformed babies in 2,850 deliveries Overall there are no significant differences between their material and our material One can however see from the table that the malformations in our series comprise 3 cases of talipes (2 3 per

Table V *Cases with Negative Hogben Test*

Series	Group	Abortion Inevitable: Pregnanediol Output: Low	Abortion Inevitable: Pregnanediol Output: Normal or Unknown	Normal Fœtuses: Pregnanediol Output: Low	Normal Fœtuses: Pregnanediol Output: Normal or Unknown	Uncertain: Pregnanediol Output: Low	Uncertain: Pregnanediol Output: Normal or Unknown	Parturition: Pregnanediol Output: Low	Parturition: Pregnanediol Output: Normal or Unknown
Series I	*Progesterone*		19 (24)				6 (10)		5 (22)
	Sedation		19 (22)		1 (4)		4 (5)		5 (24)
Series II	Progesterone	5 (8)	1 (3)	(0)	1 (3)	4 (5)	4 (5)	1* (8)	10 (36)
	Placebo	15 (15)	2 (7)	1 (2)	1 (1)	1 (3)	(3)	(4)	11* (36)

() Total in the groups
* 1 Premature labour, child died

Nowadays new and better quantitative pregnancy tests are available (Brody and Carlstrom, 1962, Wide and Gemzell, 1962) With the aid of these tests one might be able to exclude the inevitable abortions and to treat only the true threatened abortions, thus offering greater scope to test the effect of different kinds of treatments for threatened abortion *Nevertheless, ges*

Table VI *Ordinal Number of Index Abortion*

Series	Group	First Abortion	Second Abortion	Third* Abortion
Series I	Progesterone	27	6	3
	Sedation	19	7	3
Series II	Progesterone	14	5	5
	Placebo	19	10	2
	Total	79	28	13

* Three or more abortions

tagens, can be discarded as a routine treatment of cases of so-called threatened abortion

Habitual abortion

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Table VII *Malformations*

Group		Malformations	
Series I	Progesterone	Malformatio cordis	1
		Talipes	1
	Sedation	Talipes	1
Series II	Progesterone	Malformatio cordis	1
	Placebo	Talipes	1

cent) and 2 cases of malformatio cordis The corresponding numbers in the series of Hedberg *et al* were 8 (0 28 per cent) and 16, respectively

Consequently the difference in frequency of talipes between our series and that of Hedberg is highly significant ($\chi^2 = 13\ 9$)

The frequency of malformatio cordis in our series, however, does not differ significantly from that of Hedberg ($\chi^2 = 1\ 98$)

Thus a woman who has threatened to abort has a greater risk of being delivered of a child with talipes

17 ketosteroids in abortion

Bret and Ghosn (1953) and Jayle *et al* (1960) reported that when the excretion of 17-ketosteroids during pregnancy was high there was a high incidence of abortion

Table VIII *17 KS and 17 KGS Excretion in Series*

17 KS MG	Abortion	Parturition
< 15	76	90
15—20	15	23
> 20	13	11
17—KGS MG		
< 20	98	116
20—25	5	3
> 25	1	3

As the report of Bret and Ghosn seemed to be of great interest we decided to study the excretion of 17 ketosteroids and 17 ketogenic steroids in the urine of our patients with threatened abortion The values are listed in Table VIII

There was no significant difference in the incidence of abortion in relation to 17 ketosteroid excretion ($x^2 = 2\ 06$) Thus we cannot confirm the findings of Bret *et al* and Jayle *et al*

Folic acid and vitamin B12 in abortion

A number of articles concerning the malformative and arbortificative effects of folic acid deficiency and folic acid antagonists

Table IX *Whole Blood Folic Acid and Serum B12 and Iron Values in Series*

Test		Abortion	Parturition
LB Casei Activity	< 15 NG/ML	1	1
	15—25 NG/ML	4	3
	> 25 NG/ML	24	36
Str Faecalis Activity	< 1 0 NG/ML	1	3
	1 0—2 0 NG/ML	6	5
	> 2 0 NG/ML	21	3-
Serum B 12	< 90 PG/ML		
	90—180 PG ML		3
	180 PG ML	30	35
Serum Iron	50 µG 100 ML	1	
	50—90 µG 100 ML	8	33
	90 µG 100 ML	2	35

were published in the early fifties (Thiersch *et al*, 1950, Thiersch, 1952, and Thiersch, 1956)

It seemed possible that some abortions might depend on folic acid defiency in the mothers, and to elucidate this question we examined the folic acid and vitamin B12 in the blood of patients who were admitted to the hospital because of threatened abortion The only selection was the ability of the laboratory to perform the assays The iron content in the blood serum was also estimated The results are seen in Table IX The patients are classified into three groups – deficiency – borderline and normal – according to our experience in non-pregnant subjects (Hansen and v Klevesahl-Palm, 1962)

From the table it will be seen that deficiency of folic acid or B12 cannot be a common cause of abortion, if it is at all

SUMMARY

In a series of 253 threatened abortions treated with progesterone preparations or placebo and sedatives, respectively, no obvious effect of progesterone treatment could be established

There was a significant overrepresentation of children with talipes *A woman with threatened abortion during pregnancy has* a greater risk of having a child with club foot

There were no significant differences in excretion of 17-keto steroids and 17 ketogenic steroids between those who aborted and those who were delivered of viable children

There were in most of the cases tested normal blood (serum) values of folic acid and B12 and no differences between those who aborted and those who were delivered of viable children were observed

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THE TECHNIQUE OF STRASSMANN'S METROPLASTY

BY

SVEN SJÖSTEDT

The value of the Strassmann operation for plastic correction of congenital duplication of the uterus has been shown in many series of results (Jung, 1931, Philipp, 1948, Mitteldorf, 1949, Genell *et al*, 1952, Strassmann, 1952, Jones and Jones, 1953, Jones *et al*, 1956, Dunselmann, 1959, Genell and Sjovall, 1959, and Sjovall, 1960)

Schroder (1881) was the first to resect a septum in the uterus (quoted by Ruge, 1884) He performed the operation via the cervix The operation is, however, named after Strassmann who in 1903 gave a preliminary report and in 1907 a detailed description of his operative technique He united the two halves either per vaginam (8 cases) or by the abdominal route (9 cases) Later operators have, as a rule, used the abdominal route

The technique has since been modified in some respects Strassmann made a transverse incision in the uterine body and then removed the septum and united the two halves of the uterus This technique has since been recommended by Martius (1947), Steinberg (1955), Dunselmann (1959), Mathieu and Duparc (1959), Käser and Ikle (1960), and Sala and Tellini (1962), for example, while Genell *et al* (1952), Jones and Jones (1953), Te Linde (1953), Genell and Sjovall (1959), Pohjala (1959) and others prefer a sagittal incision A V-shaped incision in the uterus has been recommended by Jones *et al* (1956), and an incision in the anterior wall of

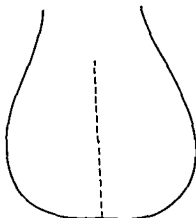


Fig 1 Uterus is incised in the midline

the uterus only, by Schmid (1930), and Palmer and Mathieu (1953) Other modifications have also been described

Special attention has been given to these duplications at the department of Gynæcology, University Hospital, Lund, where some of the technical details of the present operative procedure have been devised Since 1948 we have used this technique almost routinely

In nearly all the cases the operation was performed for corpus septum or corpus septum imperfectum with or without associated corpus arcuatum (Monie and Sigurdson, 1950) These are the commonest types in a clinical series because, as mentioned by Schulze (1937) and later by Philipp (1948), these types interfere with uterine function to a greater extent than do more complete duplications

Operative technique

The abdomen is opened by a low transverse incision The vesical fold of peritoneum is loosened and pushed down The uterine arteries are clamped with forceps in the way described by Bonney (1946) to prevent undue bleeding The ovarian arteries

Sjostedt Sven Acta obst et gynec scandinav 4 130 1963

From the Department of Obstetrics and Gynæcology (Professor A Sjovall), University Hospital, Lund, Sweden

THE TECHNIQUE OF STRASSMANN'S METROPLASTY

BY

SVEN SJÖSTEDT

The value of the Strassmann operation for plastic correction of congenital duplication of the uterus has been shown in many series of results (Jung, 1931, Philipp, 1948, Mitteldorf, 1949, Genell *et al*, 1952, Strassmann, 1952, Jones and Jones, 1953, Jones *et al*, 1956, Dunselmann, 1959, Genell and Sjovall, 1959, and Sjovall, 1960)

Schroder (1881) was the first to resect a septum in the uterus (quoted by Ruge, 1884) He performed the operation via the cervix The operation is, however, named after Strassmann who in 1903 gave a preliminary report and in 1907 a detailed description of his operative technique He united the two halves either per vaginam (8 cases) or by the abdominal route (9 cases) Later operators have, as a rule, used the abdominal route

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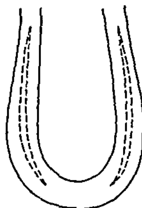


Fig 4 Wedge shaped excisions of myometrium

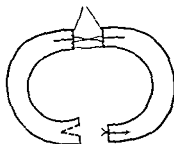


Fig 5 Figure-of-eight sutures of uterine wall

Fallopian tubes A narrow wedge shaped section is then excised from each half of the uterus (Fig 2) The width and length of the wedge depends on the extent of the septum In this way they entire septum or part of it can be removed and the uterus, which is often broad in such cases can be given normal proportions

It is advisable to open the uterus before this excision is made because it is then easier to judge how wide a piece should be excised

Any part of the septum in the cranial region is divided (Fig 3) This is preferable done over an angular (90°) forceps introduced

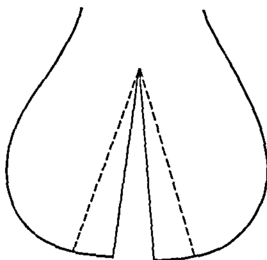


Fig 2 Septum resected

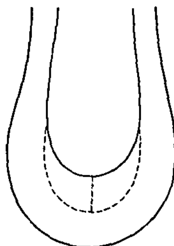


Fig 3 Residual septal tissue is divided and removed

are occluded with rubber lined clamps With these precautions it is possible to operate in an almost bloodless field

The uterus is incised in the midline (Fig 1) If the septum is long, it may be necessary to extend the incision down to the isthmus Owing to the vascular arrangement in the uterus the hæmorrhage is only slight and there is no risk of injuring the



Fig 7 a Hysterosalpingography before operation.

Results

In the years 1948–1959 thirty one cases of corpus septum or corpus septum imperfectum with or without corpus arcuatum were operated upon by the method described above The results up to 1956 are included in the data published by Genell and Sjovall Readers interested in details are referred to that paper The indications were mostly habitual abortion dysmenorrhœa or sterility

Fig 7 shows hysterograms of a patient before and after operation It is clear from the illustration that the duplication had disappeared and that the cavity is of normal shape after the operation

Twenty of the women operated upon have since had a total of

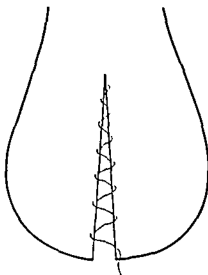


Fig 6 Continuous serosa suture

into the uterine horn Remaining parts of the septum in the uterine horn are removed Care should be taken not to damage the orifices of the tubes

From each of the four surfaces of the wounds grooves are cut from the myometrium (Figs 4 and 5) These grooves are sutured with interrupted sutures of fine catgut This irons out persistent parts of the septum and the inner surface of the cavity becomes more regular The cavity will also be larger than if the entire septum is removed These incisions in the wall are therefore particularly recommended if the cavity is relatively small or if the attachment of the anterior and posterior walls is wide

The walls of the uterus are then closed with interrupted catgut sutures In order to secure as wide an adaptation of the wound surfaces as possible without puckering figure of eight sutures are used (Fig 5) These sutures are fastened just below the submucosa and subserosa, respectively, and are not tied until all the sutures have been inserted No uterine drain is required

A continuous suture is placed in the serosa so that its surface are closely approximated (Fig 6) The anterior incision is covered with the vesical fold of peritoneum

SUMMARY

A modification of Strassmann's metroplasty is described After operation the patient can usually be delivered per vaginam and Cæsarean section should be performed only on conventional obstetric indications Of 22 vaginal deliveries in 20 women operated upon by the method the uterine wound never showed any tendency to disrupt

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Fig 7 b Hysterosalpingography after operation

29 pregnancies resulting in term delivery in 20, premature delivery in 4 and abortion in 5 Twenty-two infants were delivered per vaginam and 2 by Cæsarean section In one case the indication for Cæsarean section was placenta praevia, but in the other patient delivered by Cæsarean section the records contain no note about the indication

In no instance did the uterine wound show any tendency to disrupt

ternus with complete feminization" This group has also been analysed by Schaumkell and Stange (1956)

The appearance of the external genitalia often results in the male pseudohermaphrodite being pronounced female at birth and brought up, subsequently, as a girl During childhood there is usually little as regards physical or mental development to awaken suspicion and it is not until puberty that definite abnormalities arise menstruation fails to occur, the secondary sexual characteristics are absent or incomplete, hair growth can assume the masculine form and the voice may break The external genitalia can vary considerably, from the completely female type with normal vagina to the opposite extreme where a sinus urogenitalis is the only suggestion of a vagina The clitoris may be normal or enlarged, and the labia large and scrotum like

As regards the internal genitalia, the uterus and tubes are usually absent The testes may be found either where the ovaries are normally situated, or in the inguinal canal, or in the labia majora An inguinal hernia is frequently found

The histological appearance of the gonads is typical of that seen in a maldescended testis, having seminiferous tubules with no signs of spermatogenesis hyperplastic Leydig cells and frequent tubular adenomata The risk of malignancy in such testes is at least 20 times greater than in normal individuals (Goldberg and Maxwell, 1948 cit Young)

The psychological make up may be masculine or feminine To judge by reports in the literature, the last mentioned is most common It is the psychological sexuality rather than the genetic which determines treatment in these patients (Novak, 1935 Rubovits and Saphir, 1938 Morris 1953 Greenblatt 1955 Philipp and Staemmler, 1959)

The following is an account of two sisters with male pseudo hermaphroditism

Case 1 S H 18 years old Domestic worker

Family One sister (M.H see Case 2) and three brothers the latter normally developed according to the parents Both parents living Family history otherwise negative

Social Completed seven year primary education course – well reported on. Subsequently employed in domestic work for two years

Bergman Sven Reitalu Juhan and Sundén Bertil Acta obst. et gynec scandinav 4 138 1963

From the Institute of Bacteriology (Professor R Grubb), the Cancer Chromosome Laboratory, Institute of Genetics (Professor A Levan), and the Department of Obstetrics and Gynæcology (Professor A Sjövall), University of Lund, Sweden

MALE PSEUDOHERMAPHRODITISM IN TWO SISTERS

BY

SVEN BERGMAN JUHAN REITALU AND BERTIL SUNDÉN

Intersexuality implies incomplete sexual differentiation, and the term includes both genuine hermaphrodites and pseudohermaphrodites The latter are considerably more common than the former Genuine hermaphrodites are individuals having both testicular and ovarian tissue, either as separate gonads or combined as an ovotestis Approximately 90 such cases have been described in the literature (Lewis, 1959)

Pseudohermaphrodites have gonads of one sex and some reproductive organ of the opposite sex Two types of pseudohermaphroditism are recognised, male, and female, the former being more common According to Greenblatt (1955), male pseudohermaphroditism is a genetically acquired anatomical anomaly In such individuals the gonads and chromosomes are of male type but the bodily habitus, external genitals and psychological make up have feminine characteristics Wide variations are found, however, (v *Neugebauer, 1908) and all transitional stages* can be encountered, from the predominantly masculine type with hypospadias, to the type described by Morris (1953) as testicular feminization In this latter condition the habitus is wholly female with external genitals of female type and a vagina which is usually adequate for coitus Bottella-Llusia and Nogales (1953) labelled this type as pseudohermaphroditismus masculinus in

mation can be seen No certain ductus deferens can be identified but epididymal structures are represented. No evidence of malignancy

Diagnosis Testis with signs of atrophy (A Brun)

On 27 4 61 the patient was given the first of a series of injections of 80 mg Estradurin (polytestradiol phosphate)

Urinary hormone analysis

Date	24 Hour Urine volume in ml	Œstrogenic Substances m.u./24 Hours	FSH m.u./24 Hours	Neutral 17 KS			17 KGS mg 24 Hours
				Total mg 24 Hours	DF		
					mg 24 Hours		
4/4	800	c 100	> 40	20.4	0 3	1 5	16 3
21/4	900	< 25	> 40	8 8	0.2	2 3	14 0
26/4	1025	< 25	> 40	7 3	0.2	2 7	9.4
31/5	1650	c 100	> 40	12 8	0 6	4 7	19 3

The hormone analyses were carried out at the Hormone Laboratory Malmö General Hospital

Case 2 M H (sister of Case 1) 17 year old seamstress

Family history See Case 1

Social Completed 7 year primary education course with average reports Has since worked as a seamstress for severel years and likes this work

Previous history Underwent operation for right sided inguinal hernia when aged five The operation records do not indicate whether or not a testis was removed.

Otherwise nothing of note beyond the usual childhood ailments

Present complaint The patient sought advice at the Gynæcological Clinic because of her failure to begin menstruating

A year previously she had had a boy friend but since then she had lost interest in the opposite sex She had never attempted sexual intercourse

Physical findings (18 4 61)

Height 176 cm weight 59 3 kg

Powerfully built, but not overtly masculine Voice feminine Very slight hirsuties on upper lip but none on legs Pubic hair distribution slightly masculine Breasts quite small (Fig 3)

At the left external inguinal ring could be felt a mass about the size of a pigeon s egg This was thought to be a testicle Labia majora somewhat enlarged Clitoris moderately enlarged Posteriorly in the introitus was found a 1½ cm-wide opening leading into a 2–3 cm long blindly terminating vagina Neither uterus nor ovaries could be palpated (Fig 4)

Laparoscopy Uterus ovaries and tubes absent On either side of the

Previous history Underwent operation for left sided inguinal hernia when aged ten No indication in the operation records whether or not a testis was found or removed Otherwise nothing of note

Present complaint Three or four years ago her voice became deeper and gruffer – basso character has persisted since Because of this the patient consulted a speech therapist and was thence referred to the Gynaecological Department During the latter years there has been increasing hair-growth, particularly on the face and legs The patient has never menstruated She is not particularly attracted to the opposite sex but has had boy friends from time to time Has never attempted sexual intercourse

On examination (4 4 61)

Height 177 cm, weight 68 kg

Muscular build with relatively narrow hips and broad shoulders Hirsuties on face and legs, with slight moustache Moderate acne on chest and back Breasts small and underdeveloped Pubic hair growing up towards umbilicus in typical masculine distribution (Fig 1)

Both labia majora large and protuberant. In the right labium majus can be felt a firm, slightly tender mass the size of a pigeon s egg Clitoris enlarged – about 5 cm in length and almost as thick as a finger At the lower part of the introitus can be seen an opening approximately 5 mm wide leading into a blindly terminating vagina about 3 cm long On palpation, no internal genital organs could be detected (Fig 2)

Laparoscopy Behind the bladder could be seen two peritoneal folds reaching out laterally on each side Uterus, ovaries and tubes were absent. *No sign of genital cord could be seen*

X ray findings Pituitary fossa, suprarenals and intravenous pyelograms normal

BMR. +5%

Neuro-ophthalmological status Normal Colour vision normal

Intelligence tests Raven "Standard Progressive Matrices" gave an IQ of *100–111 IQ 116 by Terman Merrill method General intelligence* above average (B Ryde-Brandt)

Bloodgroup A Rh positive

Chromatin studies Leucocytes – 0 drumsticks per 500 cells

Skin Chromatin negative

Having regard to the patient s female up-bringing and mental make-up as well as the risk of malignant change in the maldescended testis an operation was carried out (Professor A Sjovall) on 17 4 61 In the right labium majus a *hernial* sac containing a testis was encountered The testis was removed the sac obliterated and herniorrhaphy carried out. The left inguinal canal was explored but no testis was found

Pathologist s report Macroscopically no definite epididymis or ductus deferens can be made out. Histological appearance of testis hyperplasia of the *Leydig cells* atrophy of the testicular canals with no sign of spermatogenesis and thickening of the basement membrane In one area a rete testis like for



Fig 2 S H 18 years External genitalia Large labia majora and hypertrophy of the clitoris The probe is seen entering the narrow 3 cm long vagina

Skin Chromatin negative

For the same reasons as in Case 1 an operation was performed on 27 4 61 On the left side a hernial sac was found roughly 5 cm long and containing a testis the size of a pigeon's egg Both were excised and a hernial repair was then carried out The right inguinal canal was explored but no testis was found

Pathologist's report The specimen consists of a testis with at one pole a pea sized epididymis-like structure from which a fibrous cord emerges Histologically the testis shows regular canal formation but no evidence of spermatogenesis can be seen in them. The canals are richly interspersed with Leydig cells over wide-spread areas In a section taken close to one pole can be seen a small group of cells strongly resembling so-called Berger-cells although those seen here are possibly a little smaller and less rich in cyto-

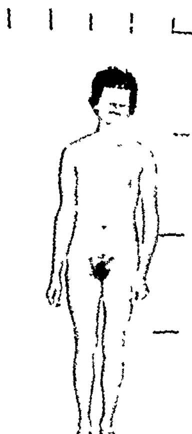


Fig 1 S H 18 years Pseudohermaphroditismus masculinus Masculine habitus and hair distribution Small underdeveloped breasts

bladder can be seen a peritoneal fold running out towards the side wall of the pelvis

X-ray findings Pituitary fossa, suprarenals and intravenous pyelograms – normal

BMR +45%

Ophthalmological status Normal Colour vision – normal

Intelligence assessment Raven Standard progressive matrices – IQ 100–111 IQ by Terman Merrill method roughly 112 General intelligence above average (B Ryde-Brandt)

Bloodgroup A Rh positive

Chromatin studies Leucocytes, possibly a couple of drumsticks (uncertain) per 500 cells



Fig 2 S H 18 years External genitalia Large labia majora and hypertrophy of the clitoris The probe is seen entering the narrow 3 cm long vagina

Skin Chromatin negative

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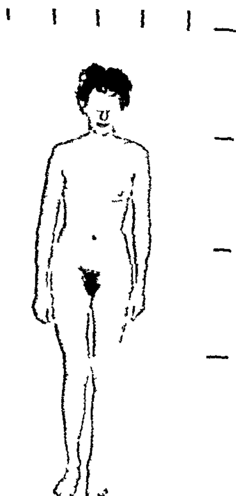


Fig 3 M H 17 years Pseudohermaphroditismus masculinus Habitus more feminine than that of sister S H

plasm. These cell groups lie closely related to a rete testis like structure In sections taken from the opposite pole, epididymal structures can be seen. Associated with the latter a tortuous ductus deferens is seen No evidence of malignancy

Diagnosis An atrophic testis with signs of Leydig-cell hyperplasia (A Brun)

On 6 5 61 the patient was given the first of a series of injections of 80 mg Estradurin (polyœstradiolphosphate)

Urinary hormone analysis

Date	24 Hour Urine volume in ml.	Œstrogenic Substances m.u./24 Hours	FSH m u./24 Hours	Neutral 17 KS			17 KGS mg. 24 Hours
				Total mg. 24 Hours	DF		
					mg/24 Hours		
20/4	400	c 25	> 40	7 7	0 2	2 6	9 9
4/5	925	< 25	> 40	8 9	0 5	5 6	13 3
12/6	800	< 25	> 40	3 8	0 6	8 2	14 2

Cytological observations Peripheral blood from both the patients and their parents was submitted to chromosome analysis (Moorhead *et al* 1960) In addition testicular tissue was cultured from both patients The great majority of cells had 46 chromosomes. In both patients and in their father the genetical constitution was XY (Fig 5) In the mother it was XX. In all of them the blood-examinations revealed two or three cells with a chromosome count of 45 instead of 46 (Table I) Analysis showed that the missing chromosome in these cells belonged to one of the chromosome groups or pairs shown in Table II Tissue-culture from the patients gonads showed no such chromosome-deficits however

Table I *Chromosome Count Distribution*

	Tissue							ΣΣ
	Blood			Testes				
	45	46	Σ	44	45	46	Σ	
Pat 1	2	67	69	–	–	54	54	123
Pat. 2	2	70	72	1	–	50	51	123
Mother	2	51	53	–	–	–	–	53
Father	3	64	67	–	–	–	–	67

Table II *Lost Chromosomes*

	Counted Cell with 45 Chromosomes	Group or Number of Lost Chromosomes Tissue Blood
Pat 1	2	21 21
Pat. 2	2	13–15 21
Mother	2	5 X 6–12
Father	3	3 X 6–12 21

Discussion

A number of writers have published descriptive reports of cases of pseudohermaphroditism, and have commented on the familial tendency in this condition (Mishell, 1938, Witschi and Mengert, 1942, Morris, 1953, Philipp and Staemmler, 1959) No case of intersexuality was found in the present family, however Pettersson and Bonnier (1937) pointed out that the condition of testicular feminization may be associated with a sex-linked recessive or a sex-limited autosomal dominant gene The same conclusion was reached by Grumbach and Barr (1958) who further consider that apparent females with testicular feminization are, in reality, sex-reversed males

Lejeune *et al* (1960) studied bone marrow cells from three patients and found chromosome counts of 46 and an XY genetic constitution

Jacobs *et al* (1959) reported similar results from four cases Their chromosome counts varied at about 46, the variations being due, according to the author, to artefact arising during the preparation of the material Our chromosome counts from blood culture material showed occasional deficits, being 45 instead of 46 This occurred not only in both patients but also in both parents Analysis of the deficient cells showed that one of the next-smallest acrocentric chromosomes – no 21 – was absent on two occasions in patient 1, on one occasion in her sister, patient 2, and on one occasion in their father This abnormal chromosome-pattern was not seen in the testicular cells from either of the patients

Both sisters had been brought up as girls and both had typically female occupations Their psychological make-ups were also entirely feminine

The bodily habitus presented masculine features in both patients, even though in Case 2 the feminine were dominant The external genitalia were clearly intersexual in both

As adjudged by the gonads both patients were men Both had obviously had a testicle removed at an earlier date, and in both, the histological appearance of the remaining gonad coincided with findings from similar cases reported in the literature, namely



Fig 4 M H 17 years External genitalia Enlargement of the labia majora and moderate hypertrophy of the clitoris The probe indicates the vaginal introitus

atrophy with absent spermatogenesis and Leydig-cell hyperplasia No signs of malignancy were found Laparoscopic examination of the pelvis confirmed the clinical impression that the internal genitalia were absent (This is a simple method causing the patient minimal upset)

Information in the literature regarding urinary œstrogens and FSH in pseudohermaphrodites is somewhat conflicting There is evidence that œstrogens are produced in the testis but opinion is divided as to which cells are responsible for their production (Diczfalusy and Lauritzen, 1961) Thus Rubovits and Saphir (1938) found gonadotrophins and not œstrogens

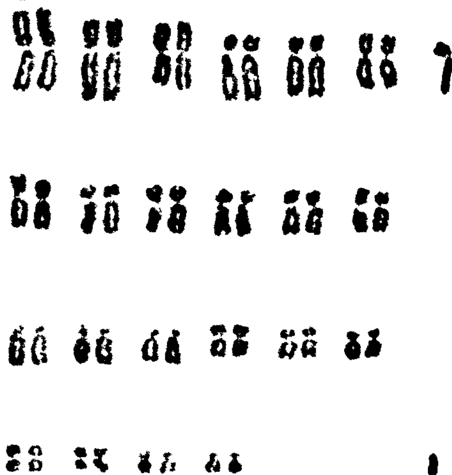


Fig 5 Karyotype of pat S H

Mishell (1938), and Witschi and Mengert (1942) demonstrated normal œstrogen-titres but low gonadotrophin-titres prior to orchidectomy, and the reverse afterwards Finkler (1948) and similarly Greenblatt (1955) described cases with hypoœstrogenism

The œstrogen-titre (estimated by the method of Allen Doisy) in our first case showed a high value initially, which fell after castration In Case 2, as would be expected, the œstrogen-titre was low even prior to extirpation of the testis It was difficult to judge whether, in Case 1, the high titre was due to testicular

œstrogen production, or, having regard to the high (for women) 17 KS and 17 KGS values to suprarenal hyperactivity Castration may result in climacteric symptoms, which is one of the reasons for giving œstrogens

Hain and Schofield (1947), and Hamblen *et al*, (1951) have described cases with high gonadotrophin titres Castration and to a lesser degree, cryptorchidism, probably act on the pituitary gland via inhibition of an inhibitory hormone, possibly œstrogen, resulting in increased production of FSH The gonadotrophin titre (Hamburger s modified method) was, in both our cases, higher than normal

The 17 KS values cited by the previously quoted writers have been normal In our second case, the 17 KS values (determined by Callow and Jensen s method) and the 17 KGS values (Norymberski s method) fall within normal limits The corresponding values are, in Case 1, initially above normal for women, but normal for men Case 1 also had more masculine features than Case 2 The DF indices (dehydroepiandrosteron fraction, determined by the Jensen Tötterman method) are normal for females

As pointed out earlier, it is the psychological sex of the patient, and not the genetic sex, which is of primary importance when planning treatment In both the patients herein described, the disposition is entirely feminine, and this state of affairs must be preserved Removal of the testis was dictated mainly by this consideration but also by the risk of malignancy Both patients will continue to be given œstrogens in order to increase feminization Such treatment usually leads to reduction in the size of the clitoris At a later stage an attempt will be made to provide the patients with a vagina adequate for coitus

SUMMARY

An account is presented of two sisters with male pseudohermaphroditism Each had one testicle hypertrophy of the clitoris and a rudimentary vagina Both completely lacked internal genitalia Hormone and chromosome analyses were carried out and the results of these are discussed The genetic constitution was XY in both patients Both were entirely female in psychological

make-up The importance of the latter, rather than the genetic sex, is stressed as being the determining factor in treatment

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ON THE VASCULATURE OF ECTOPIC ENDOMETRIUM WITH DECIDUAL REACTION

BY

USKO NIEMINEN

It is well known that the same type of structural changes take place in endometriosis during the cycle as those occurring in the endometrium The degree of the cyclic changes depends on the site of the endometriosis (Chydenius, 1935) and on the amount of stromal tissue present. The less stroma around the glands the slighter the cyclic changes (Schereschewsky, 1931) In the absence of stroma changes in the glandular epithelium may be entirely lacking (von Numers, 1942)

During pregnancy endometriotic tissue usually undergoes de cidual changes similar to those occurring in normal endometrium (Lissowetsky and Bujko, 1932 Seitz, 1932 and Heim, 1959) but according to Albrecht (1955) this is not invariable Incomplete decidual (pseudo-decidual) reaction may arise from the hormonal influence of the corpus luteum, whether or not this is associated with pregnancy (Schereschewsky, 1931)

Changes of the same nature occur in the blood vessels of endo metriosis during the cycle as those in the blood vessels of the endometrium (Nieminen 1962) Saito (1926), Wiegand (1930) and Ramsey (1955) noted that the changes occurring in the blood vessels of the endometrium during pregnancy differ from cyclic changes It is highly probable that changes occur in the blood vessels of endometriosis during pregnancy similar to those occurring in the endometrium



Fig 1 Coiled arteriole straight venule and transverse section of dilated venule Haemat – van Gieson × 120

Material and Method

The material was obtained from specimens sent to the laboratory of the Departments of Obstetrics and Gynæcology I and II, Helsinki University Central Hospital The specimens were taken from endometriotic lesions removed during operation from four different patients and numbered 9 in all In three patients the specimens were taken from the ovaries and in the remaining case from the Fallopian tube The ovarian specimens were taken in the 2nd–3rd month of intra-uterine gestation and the tubal specimens in the 3rd month of tubal gestation

The specimens, preserved in a 10 % solution of formalin for 1 to 2 days, were dehydrated in solutions of alcohol and xylol



Fig 2 The same arteriole as in Fig 1 divides into two branches Haemat – van Gieson. × 300

They were then embedded into paraffin blocks from which serial sections of 6 μ and separate sections of 30 μ were cut with a microtome The hæmatoxylin van Gieson schedule was used as standard staining procedure For the elastic tissue staining Weigert s method was used while the reticulin fibres were stained by Foot s silver impregnation process

Drawings were made of the blood vessels from consecutive serial sections By comparing the drawings an idea of the position and direction of the blood vessels in endometriosis was obtained

a *Decidual Reaction in Endometriosis during Pregnancy*

The degree of the decidual changes in endomeriotic lesions is variable In flat lesions or in those growing along the surface also in small lesions the changes are incomplete only secretory changes or pseudo-decidual reactions are seen Free growing



Fig 1 Coiled arteriole, straight venule and transverse section of dilated venule Haemat - van Gieson × 120

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The specimens, preserved in a 10 % solution of formalin for 1 to 2 days, were dehydrated in solutions of alcohol and xylol



Fig 4 Arteriole entering the endometriosis in a straight line also venules Haemat. – van Gieson. × 40

extend right up to the vicinity of the surface epithelium The lumen of the arterioles is in general compact but in the superficial parts of the lesion slight dilatation appears here and there In the pars basalis and above it the arterioles are for the most part coiled (Figs 1 2 and 3) even though the same arteriole may then continue almost straight The arterioles have branches and frequently divide above the pars basalis into 2 to 3 branches of the same magnitude (Figs 1 and 2)

According to Ramsey (1955) the tortuosity of the coiled arteries in a decidual endometrium diminishes during pregnancy while dilatation occurs in the neighbourhood of the intervillous spaces



Fig 3 Coiled arteriole slightly sinuous venule and transverse section of dilated venule Haemat – van Gieson × 1?0

lesions (Nieminen 1962) and those containing abundant stroma become decidual in the same manner as the endometrium However, decidual reaction is lacking in the narrow zone of the bordering tissue (pars basalis) (Figs 1 2 3 and 4)

Glands are scanty or absent in endometriosis showing decidual reaction With silver impregnation staining only dark points are seen and these are for the most part accumulated around the blood vessels

b *Topography of the Blood Vessels*

The course of an arteriole in decidual endometriosis may be markedly coiled slightly tortuous or straight The arteriolar apices



Fig 4 Arteriole entering the endometriosis in a straight line also venules Haemat. van Gieson. × 40

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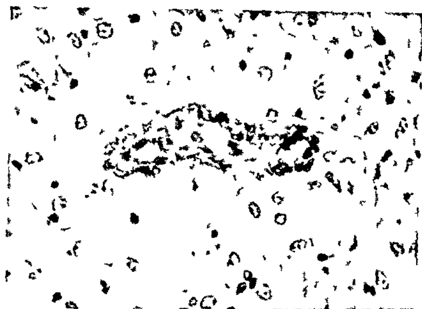


Fig 5 Transverse sections of arteriole Haemat — van Gieson × 400

The densest capillary network of decidual endometriosis lies adjacent to the surface epithelium Capillary dilatation is general but predominates in the vicinity of the surface epithelium

The stems of venules in the larger lesions and also the venules of the network are often straight The venular stem may follow a completely straight course from the pars basalis to the subjacent area of the epithelium (Fig 4) The venules in the superficial parts of the lesions are greatly dilated

According to Ramsey (1955) the number of veins in decidual endometrium diminishes during pregnancy and the veins are extremely dilated

c *The Structure of the Blood vessels*

The arterioles in decidual endometriosis are strong in structure and differentiate clearly from surrounding stroma tissue (Fig 5) The nuclei of the endothelial cells are long and pale The increased proliferation found by Ramsey (1955) in the coiled arteries of decidual endometrium is not seen in the endothelial cells of decidual edometriosis The media of the arterioles comprises 1 to 2 layers of muscle fibres, among which there are

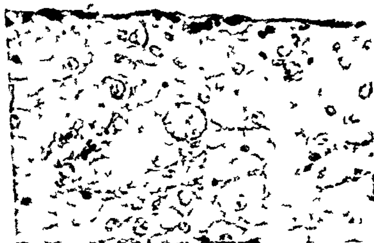


Fig 6 Transverse sections of capillaries near the surface epithelium of endometriosis Haemat. van Gieson. × 400

a few collagen fibres The latter may however be absent The adventitia is fairly strong but not so compact as in arterioles in the tissue surrounding the endometriosis The adventitia is formed of collagen fibres in 2 to 3 layers which stain well and homogeneously In the arteriole walls there are extremely weak and poorly staining elastic fibres which do not form coherent membranes *Saito (1926) and Wiegand (1930)* observed that the elastic fibres of the coiled arteries in decidual endometrium increase and strengthen (Graviditatssklerose)

The walls of the capillaries are formed almost entirely of endothelial cells and pericytes (Fig 6) Here and there in the capillary walls some collagen fibres and a few weak poorly staining elastic fibres are seen In dilated capillaries the endothelial cells and their nuclei are elongated (Fig 6) In addition the nuclei are dark and small The walls of dilated capillaries are however compact

In the venular walls there are a few collagen fibres in addition to the endothelial cells but generally in only 1 or 2 layers The elastic fibres are weak and do not form coherent membranes In dilated venules the endothelial cells and their nuclei are elongated

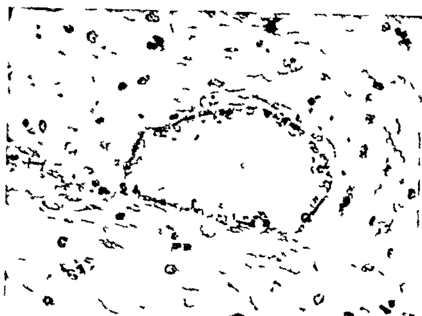


Fig 7 Transverse section of dilated venule Haemat. - van Gieson X 400

and dark in colour (Fig 7) The wall of this type of venule is thin but compact

Discussion

The degree of decidual reaction in endometric lesions during pregnancy is variable and depends, as do the cyclic changes, on the amount of stroma and on the manner of growth of the endometriosis in the surrounding tissue

It is highly probable that the forming of decidua is also dependent on duration of the pregnancy As the pregnancy continues decidua subsequently forms in more slowly reacting lesions

The topography of blood vessels in decidual endometriosis resembles that of the blood vessels in endometriosis during the early secretory phase, but coiled arterioles are less numerous Dilatation of the capillaries and venules occurs mainly near the surface epithelium of the lesions

The blood vessels of the decidual endometriosis are strong in structure, corresponding to the structure of the blood vessels of endometriosis in the early secretory phase The same type of proliferation of endothelial cells is not observable in the arterioles

as in the coiled arteries of the endometrium during pregnancy The elastic fibres of arterioles, capillaries and venules are so weak, both in endometriosis not associated with pregnancy and in decidual endometriosis, that possible slight strengthening and increase in the fibres is not demonstrable

SUMMARY

The author has studied the vasculature of decidual endometriosis during pregnancy In both the topography and structure of the blood vessels changes are observed which differ from changes occurring during the menstrual cycle

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THE EFFECT OF EPSILON-AMINOCAPROIC ACID ON UTERINE HÆMORRHAGE

BY

OLE K ALBRECHTSEN AND PREBEN SKJØDT

The occurrence of fibrinolytic components in the human endo metrium has been known since 1910 (Halban and Frankl) Later investigations have shown that the fibrinolytic power of the endometrium varies with the menstrual cycle and is strongest in the luteal phase Endometrial tissue from before the menarche and after the menopause shows no fibrinolytic activity (Caffier, 1930, Page, Glendening and Parkinson, 1951) Finally, in vestigations published in 1956 showed that the power of the endo metrium to break down fibrin substrates is due to a plasminogen activator, which on contact with fibrin is capable of converting the plasminogen occurring in the fibrin to the active fibrinolytic en zyme, plasmin (Albrechtsen, 1956a, Philips, Butler and Taylor, 1956)

The human endometrium also contains tissue thromboplastin (Bell, 1913, Whitehouse, 1914) Saline extracts of endo metrial tissue are thus capable of shortening the coagulation time for normal plasma

The importance of the plasminogen activator and the tissue thromboplastin in uterine bleeding has been discussed in several

Epsilon aminocaproid acid was supplied through the courtesy of A/S GEA Copenhagen

papers (Whitehouse, 1914, Albrechtsen, 1956a, Elert and Nold, 1956) The view has been expressed that both components are liberated from the endometrium during normal menstruation and in pathological uterine hæmorrhage The tissue thromboplastin is assumed to cause intra uterine coagulation with simultaneous consumption of factor I (fibrinogen), factor V (proaccelerin), factor II (prothrombin) and factor VII (proconvertin), thus playing a part in the limitation of bleeding while the plasminogen activator by transforming blood plasminogen into the active fibrinolytic enzyme, plasmin, should cause a dissolution of the formed clot The demonstration of thromboplastic activity (Cristea and Denk, 1910, Whitehouse, 1914) and of plasminogen activator (Albrechtsen 1956b) in menstrual blood lends support to this view However, Beller and Graf (1957) advanced the theory that during normal menstruation intra uterine formation of fibrin does not occur, but that the plasminogen activator by converting plasminogen into plasmin directly, gives rise to a breakdown of factor I (fibrinogen) and of factor V, factor VIII (antihæmophilic globulin A) and factor II On the other hand it is generally agreed that the incoagulability of menstrual blood is due to lack of factor I and that this local afibrinogenæmia must be related to the increased fibrinolytic activity

It is as yet unknown whether the endometrial plasminogen activator plays a part in the mechanism of menstruation by inducing bleeding from the mucosa at the time of menstruation

In 1957 Japanese workers found that epsilon aminocaproic acid (EACA) inhibits the fibrinolytic process (for references see Nilsson Bjorkman and Andersson 1961) Later studies have shown that this effect is mainly due to inhibition of the conversion of plasminogen into the active fibrinolytic enzyme plasmin (Ablondi and Hagan 1958 Ablondi Hagan Philips and De Renzo 1959 Alkjærsig Fletcher and Sherry 1959) It must be assumed that a weak anti plasmin effect is also at work This observation is the basis for the use of EACA in the treatment of hæmorrhagic diatheses associated with increased fibrinolytic activity in the circulating blood In addition certain investigations seem to show that EACA is capable of counteracting local fibrinolytic processes Thus the drug has been

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reported to have a beneficial effect on uterine hæmorrhage (for references, see Nilsson, Bjorkman and Andersson, 1961) The present paper is a report of a study of this effect

Methods

Samples of both venous and vaginal blood were collected in tubes (14 × 100 mm) with potassium ammonium oxalate 2 5 % (Wintrobe) as the anticoagulant (ratio 10 1) and at once centrifuged at 3,500 RPM for 15 minutes The plasma was then stored at −20° C for subsequent determination as enumerated below

1 Prothrombin time by the method of Quick (1935)

2 Factor V (proaccelerin) by the method of Koller, Loeliger and Duckert (1951)

3 Factors II and VII (prothrombin, proconvertin) by the method of Owren and Aas (1951)

4 Thromboplastin generation by the method of Hicks and Pitney (1957) In this test, 0 5 ml platelet substitute is added to 0 5 ml dilute plasma derived from blood from an arm vein or from the vagina After incubation for 60 seconds 0 5 ml calcium chloride is added In this mixture, plasma thromboplastin is formed from the precursors factor VIII (anti hæmophilic globulin A), factor IX (anti hæmophilic globulin B, Christmas factor), factor XI (plasma thromboplastin antecedent, PTA), factor XII (Hageman factor), since excessive quantities of the platelet factor and calcium are present The concentration of the plasma thromboplastin formed is assayed by adding 0 1 ml of this mixture and 0 1 ml normal platelet-deficient plasma, after which the coagulation time is determined By performing this determination at two minute intervals, an expression of the rate of formation of the plasma thromboplastin is obtained In a normal person, coagulation times of constantly decreasing length will be obtained, indicating a constantly increasing concentration of plasma thromboplastin, whereas in persons in whom one of the above mentioned factors is absent, delayed and diminishing formation of plasma thromboplastin will occur If thromboplastin is present at the beginning of the analysis, this will be manifested by a reduced coagulation time even at the first determination

5 In comparative studies of vaginal and peripheral blood from the same patient, the difference in thromboplastic activity was estimated by determining the recalcification time in a mixture of dilute patient plasma and hæmophilia A or hæmophilia B plasma As the content of factor VIII or factor IX is considerably reduced in plasma from patients suffering from hæmophilia, the ability of such plasma to form thromboplastin will be reduced In an incubation mixture such as that described here, the coagulation time after recalcification will therefore be determined by the thromboplastic activity of the plasma added An amount of 0 1 ml vaginal plasma diluted with veronal buffer in the ratio 1 10 was incubated with 0 1 ml undiluted hæmophilia A plasma at 37° C for 60 seconds, 0 1 ml calcium chloride was then added, and the coagulation time was determined. Similar determinations were performed with hæmophilia B plasma

6 Factor I (fibrinogen) was determined by addition of 1 ml plasma to 60 ml physiological saline, coagulation with 1 ml thrombin (100 NIH/ml) in saline, standing for 1 hour, rolling on a glass rod degreasing with alcohol and ether, desiccation at 110° C for 1 hour and weighing

7 The fibrinolytic activity in the plasma was determined by the fibrin plate method (Astrup and Müllertz, 1952) Drops of 0 03 ml of plasma were placed on a thin layer of bovine fibrin in a Petri dish, and the fibrinolytic activity was expressed by the area of the digested zone of the fibrin after incubation at 37° C for 18 hours (average of three determinations) Preceding heating of the fibrin plate at 85° C for 35 minutes destroys the plasminogen normally present in the plate without a simultaneous destruction of the fibrin (Lassen 1952) This makes it possible to distinguish between activity caused by plasminogen activators and activity referable to the fibrinolytic enzyme plasmin since only plasmin activity is measured on heat treated plates, whereas the combined effect of plasminogen activators and plasmin is measured on ordinary plates

8 The endometrium was analysed by means of a modification of the method for quantitative determination of the stable tissue plasminogen activator described by Astrup and Albrechtsen (1957) The tissue was crushed and a 2M solution of potassium

reported to have a beneficial effect on uterine hæmorrhage (for references, see Nilsson, Björkman and Andersson, 1961)

The present paper is a report of a study of this effect.

Methods

Samples of both venous and vaginal blood were collected in tubes (14 × 100 mm) with potassium ammonium oxalate 2.5% (Wintrobe) as the anticoagulant (ratio 10 : 1) and at once centrifuged at 3,500 RPM for 15 minutes. The plasma was then stored at −20° C for subsequent determination as enumerated below.

1. Prothrombin time by the method of Quick (1935)

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end of the treatment. Side effects in the form of nausea vomiting dizziness and diarrhœa were present. Histological diagnosis early follicular phase

Case 2 – 32 years (35/62–63) Irregular and lately profuse menstrual periods for three years Two months before admission curettage without effect Histological diagnosis follicular phase Vaginal examination fresh bleeding An ovarian cyst 8 × 6 cm was palpated to the right of the uterus EACA mixture was given six times after which the bleeding stopped Slight nausea and dizziness occurred Curettage was not performed

Case 3 – 48 years (43/62–63) Irregular and profuse menstrual periods for several years Curettage performed two and one year previously had revealed irregular hyperplasia The periods persisted unchanged Vaginal examination fresh bleeding A small erosion was seen on the portio vaginalis The uterus was felt to be plump and firm EACA was given six times resulting in complete cessation of the bleeding Nausea and dizziness occurred Histological diagnosis menopausal endometrium

Case 4 – 26 years (52 62–63) Irregular and profuse menstrual periods for six years Curettage had been performed on four occasions last time 18 months previously but had had only transient effect. Vaginal examination fresh bleeding from the external os otherwise no abnormalities EACA was given six times resulting in complete cessation of the bleeding No side effects were observed Histological diagnosis follicular phase

Case 5 – 43 years (82/62–63) Menometrorrhagia for three years The bleeding had become more profuse during the last four months Curettage had been performed a fortnight previously Histological diagnosis follicular phase Profuse bleeding on admission Vaginal examination violent bleeding with the passage of small blood clots The uterus was plump EACA was given six times after which the bleeding stopped. The patient was mildly nauseated and vomited once Curettage was not performed

Case 6 – 44 years (107/62–63) Menometrorrhagia for four years Curettage had been performed twice last time four months previously Histological diagnosis incipient luteal phase Since then more profuse and more prolonged hæmorrhages had occurred Vaginal examination fresh bleeding with a few clots The uterus was a little plump EACA given six times resulted in complete cessation of the bleeding Discomforts in the form of headache and nausea occurred Histological diagnosis early follicular phase

Case 7 – 43 years (142/62–63) Metrorrhagia for eight years with more profuse menstrual periods during recent years Curettage had been performed on four occasions last time in November 1961 Histological diagnosis mild irregular hyperplasia. Since then the metrorrhagia continued Vaginal examination moderate bleeding The uterus was plump and fibromatous EACA was given 11 times At the end of the treatment the bleeding had abated appreciably but it had not ceased Slight nausea occurred Total hysterectomia was performed Histological diagnosis irregular glands with occasional secretion

Case 8 – 47 years (166 62–63) Menometrorrhagia for about 12 months

thiocyanate (30 ml/1000 mg tissue) was added This mixture was then gently shaken for 2 hours After centrifugation, 1 ml of the supernatant was diluted with 7 ml distilled water and precipitated with 1N hydrochloric acid down to pH 1 After renewed centrifugation, the sediment was dissolved in 1 ml potassium thiocyanate and neutralised with sodium bicarbonate with litmus paper as the indicator This solution contains the plasminogen activator, if any, from the endometrial tissue but, unlike the original method, the modification does not give a quantitative extraction However, the modified method is useful for the demonstration of plasminogen activator of the stable tissue activator type The fibrinolytic activity in the extract was determined both on heat treated and ordinary fibrin plates as described above

Clinical Series

The series studied consisted of 15 patients who were admitted because of menometrorrhagia If bleeding was absent at the time of admission, the patient was discharged with the instruction to return as soon as menstruation occurred A vaginal examination was then performed, and at the same time specimens of blood from the vagina and from an arm vein were obtained for analysis Treatment with EACA mixture, 0 1 g/ml, (KABI) was then instituted A dose of 30 ml was given every fourth hour, and after 24 hours a second vaginal examination was performed If this, and close observation during the period of treatment, showed that the bleeding had ceased, curettage was performed, and a blood sample was withdrawn from an arm vein The removed endometrial tissue was subjected to chemical analysis and histological examination

Case Reports

Case 1 - 42 years (2011/61-62) Bleeding for 10 days every 28 days for the preceding 2 years Vaginal examination showed profuse fresh bleeding with a single small clot otherwise normal conditions On the second day of bleeding EACA mixture was given six times After the administration of 60 ml, the bleeding abated appreciably and it had ceased completely at the

the posterior wall of the corpus uteri The growth measured 5 × 5 cm and was covered by a layer of firm clotted blood about 5 mm in thickness

Case 14 – 28 years (278 62–63) Irregular periods for two years Curettage had been performed twice last time seven months before admission. Histological diagnosis follicular phase Since then regular but very profuse menstrual periods had occurred. Vaginal examination fresh bleeding but otherwise normal conditions EACA was given six times after which the bleeding stopped The patient was seriously troubled by headache nausea and diarrhœa Histological diagnosis follicular phase

Case 15 – 36 years (332/62–63) Irregular bleeding for 10 years Curettage had been performed on three occasions last time three years before admission Vaginal examination profuse fresh bleeding with small clots otherwise no abnormalities EACA was given six times The bleeding stopped at the end of the treatment. The patient experienced side effects in the form of headache dizziness and nausea Histological diagnosis incipient luteal phase

Results

The results of the prothrombin determinations by the method of Quick are shown in Figure 1 A The values for peripheral blood were normal both before and after the treatment with EACA In all the samples of vaginal blood studied the Quick value was 0 per cent

The concentrations of factor V are shown in Figure 1 B The concentrations in the peripheral blood before and after EACA treatment were unchanged and within the range of normal variations Vaginal blood examination showed minimal amounts of factor V

Similar results were obtained in the determination of the factors II and VII (Fig 1 C) Thus normal and uniform values before and after EACA treatment were obtained The concentrations of the factors II and VII in vaginal blood were low

The thromboplastin generation test was performed on peripheral blood before treatment in 10 cases Similar studies were performed on 10 samples of vaginal blood and four samples of peripheral blood after treatment A typical example is shown in Figure 2 It is seen that whereas rapid and uniform formation of plasma thromboplastin occurred in peripheral blood with maxima after 5–7 minutes both before and after treatment, vaginal blood did not show any formation of thromboplastin On the

Curettage performed six months previously had been ineffective Histological diagnosis menopausal phase *Since then, irregular bleeding had persisted.* Vaginal examination fresh bleeding, otherwise normal conditions EACA was given five times, resulting in complete cessation of the bleeding No side effects Histological diagnosis incipient luteal phase

Case 9 – 23 years (105/62–63) Since a normal delivery 15 months previously, frequent and profuse hæmorrhages had occurred which during the three months preceding admission lasted about 20 days each Vaginal examination fresh bleeding otherwise normal conditions EACA was given six times, resulting in complete cessation of the bleeding without any discomforts Histological diagnosis endometrium with some secretion

Case 10 – 36 years (207/62–63) Increasing menorrhagia for 10 years Vaginal examination fresh bleeding otherwise normal conditions EACA was given six times after which the bleeding stopped Moderate nausea was present Histological diagnosis incipient secretion in some areas

Case 11 – 38 years (212/62–63) Irregular menstrual periods of fluctuating intensity for 15 years Curettage had been performed on ten occasions last time about 12 months previously Histological diagnosis follicular phase The patient was then given chorionic gonadotrophin treatment (Physex LEO) resulting in regular menstrual periods This treatment was discontinued four months before admission, following which irregular and profuse hæmorrhages reappeared Vaginal examination fresh bleeding otherwise normal conditions After having received EACA twice, the patient suddenly became seriously ill with dyspnœa, periorbital œdema, generalised urticaria and paræsthesiæ of the hands These reactions disappeared after injection of calcium and antihistamine (Antistina CIBA) At this time very sparse vaginal bleeding was observed Curettage was performed 24 hours later Histological diagnosis follicular phase

Case 12 – 26 years (269/62–63) The menstrual periods had been very profuse and sometimes irregular, during the last six years Curettage had been performed twice, last time 18 months previously Histological diagnosis follicular phase However, irregular and profuse bleeding continued Vaginal examination fresh bleeding otherwise no abnormalities EACA was given five times after which the bleeding stopped No discomforts developed Histological diagnosis early follicular phase

Case 13 – 44 years (277/62–63) Profuse prolonged, but regular menstrual periods had occurred during the preceding 10 months Curettage performed six months previously had shown follicular phase In spite of treatment with Physex profuse bleeding continued The uterus was plump but otherwise no abnormalities were disclosed It was therefore decided to perform hysterectomy However as vaginal examination revealed fresh bleeding with fairly large clots EACA treatment was instituted Seven doses were given The EACA treatment resulted in cessation of the bleeding Side effect in the form of violent diarrhœa developed Hysterectomy was performed the next day The uterus contained a slightly pedunculated submucous fibromyoma arising from



Fig 2 Thromboplastin generation in the peripheral blood before and after treatment with EACA compared with thromboplastin generation in the vaginal plasma before the treatment with EACA (case 15)

●———● peripheral plasma before treatment
○———○ peripheral plasma after treatment
———△ vaginal plasma before treatment

Table I *Recalcification Time for an Incubation Mixture Consisting of 0 1 ml Plasma and 0 1 ml Hæmophilia A Plasma For Details See Text*

Record No.	Plasma from Vaginal Blood (sec)	Plasma from Peripheral Blood (sec)
2011 61–62	174	126
43 62–63	89	154
52 62–63	92	179
82 62–63	134	115
107 62–63	71	200
142 62–63	67	148
166 62–63	30	142
195 62–63	58	199

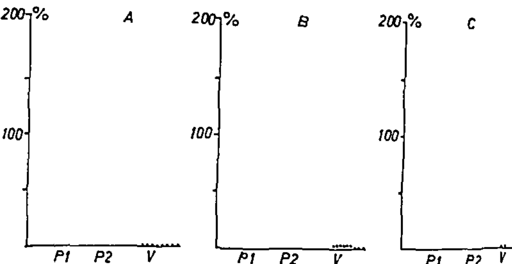


Fig 1 The concentrations of the coagulation factors in the peripheral blood before treatment with EACA (P1) and after its termination (P2) and in the vaginal blood before the treatment with EACA (V)

A, prothrombin time by the method of Quick in %
B, factor V (proaccelerin) concentration, in %
C, concentration of the factors II and VII (prothrombin proconvertin), in %

other hand, at the beginning of the experiment, the thrombo plastin concentration was higher in vaginal than in peripheral blood, possibly indicating that tissue thromboplastin had been liberated from the endometrium during the bleeding

In order to confirm the presence of thromboplastic activity in vaginal blood a number of determinations of the recalcification time were performed on dilute plasma both from vaginal and peri pheral blood and hæmophilia-A plasma The results are shown in Table I In six of the eight analyses, the coagulation time for vaginal blood was appreciably shorter than for peripheral blood Similar experiments were performed with hæmophilia B plasma The results appear from Table II In seven of the eight analyses, the coagulation time for vaginal blood was considerably shorter than for peripheral blood

The concentration of factor I (fibrinogen) in the peripheral blood was normal at the beginning of treatment and remained unchanged at the end of treatment (Fig 3 A) The collected



Fig 2 Thromboplastin generation in the peripheral blood before and after treatment with EACA compared with thromboplastin generation in the vaginal plasma before the treatment with EACA (case 15)

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82/62–63	134	115
107/62–63	71	200
142/62–63	67	148
166/62–63	30	142
195/62–63	58	199

Table II *Recalcification Time for an Incubation Mixture Consisting of 0 1 ml Plasma and 0 1 ml Hæmophilia B Plasma For Details, See Text*

Record No	Plasma from Vaginal Blood (sec)	Plasma from Peripheral Blood (sec)
2011/61–62	144	110
43/62–63	92	201
52/62–63	118	225
82/62–63	94	143
107/62–63	84	170
142/62–63	83	136
166/62–63	30	180
195/62–63	75	263

amounts of vaginal blood were insufficient for the determination of the concentration of factor I, but it is known from previous investigations that vaginal blood does not contain fibrinogen (Whitehouse, 1914, King, 1921, Lozner, Taylor and Taylor, 1942, Erf, 1952, Elert and Nold, 1956) In addition, it must be emphasised that the above-mentioned determinations of the prothrombin time on vaginal blood, which does not clot on addition of thromboplastin and calcium, unquestionably demonstrate the absence of fibrinogen

Measurements of the activity of untreated plasma from peripheral blood on heat-treated plates did not reveal any plasmin before or after the EACA treatment In contrast to this, some plasmin activity was disclosed in vaginal blood from six of the 15 patients studied (Fig 3 B)

The activity observed on the ordinary fibrin plates is shown in Figure 3 C One sample of peripheral blood showed a very moderate activity before the commencement of treatment, while the remaining samples were inactive After the termination of treatment, the activity in the positive sample had disappeared, and the others remained inactive In contrast with this observation, all but three samples of vaginal blood were active Two of the inactive samples originated from patients in whose vaginal blood large blood clots had been observed It is possible that fibrinolytically active components, if any, in these two cases may

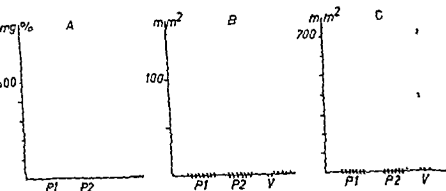


Fig 3 The content of fibrinogen and fibrinolytically active components in the peripheral blood before treatment with EACA (P1) and after its termination (P2) and in the vaginal blood before treatment with EACA (V)

A factor I (fibrinogen) in mg%
B fibrinolytic activity on heat treated fibrin plates in mm
C fibrinolytic activity on ordinary fibrin plates in mm²

have been bound to the fibrin, so that they could not be determined

Studies of the endometria showed that all samples contained plasminogen activator after the termination of treatment, since in all cases activity was observed in measurements on ordinary plasminogen-containing fibrin plates while no activity was revealed when the same solutions were placed on heat treated, plasminogen free plates (Fig 4) The areas of the digested fibrin zones on the plates varied within wide limits from case to case, indicating considerable variation in the concentrations of plasminogen activator

Supplementary Experiments

In order to study if EACA is capable of inhibiting the plasminogen activator which has been revealed in endometrial tissue in previous investigations the following experiment was performed

An extract of fresh endometrial tissue was made as previously

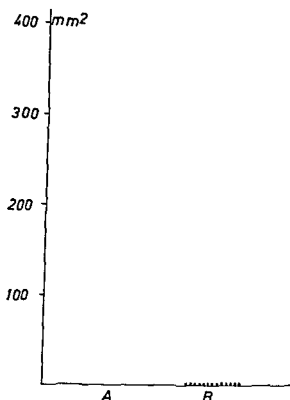


Fig 4 The fibrinolytic activity of the endometrium measured on (A) ordinary fibrin plates and (B) heat treated fibrin plates in mm

described To 0 1 ml of this solution was added 0 1 ml of EACA solution in various concentrations (1 0, 0 8, 0 6, 0 4, 0 2, 0 1 and 0 05 %) The samples were allowed to stand at room temperature for 30 minutes, and the activity of various solutions was then measured on ordinary fibrin plates A typical example is shown in Figure 5 It is seen that increasing concentrations of EACA result in decreasing activity of the plasminogen activator

Similar experiments were performed on vaginal blood After centrifugation and removal of the supernatant, 0 1 ml plasma was added to 0 1 ml EACA solution in the concentrations just mentioned After incubation at room temperature for 30 minutes, the activity of the various samples was measured on ordinary plates The results are shown in Figure 6 In this experiment, EACA in a

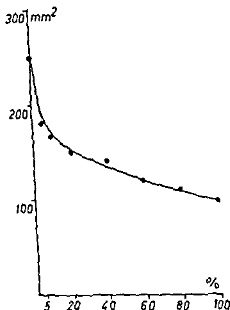


Fig 5 The inhibitory effect of EACA on the plasminogen activator of the endometrium For details see text – Abscissa concentration of EACA as a percentage of the stock solution – Ordinate digested zone in mm

solution of 0 4 % gave complete inhibition of the plasminogen activator present in vaginal blood

Discussion

Profuse and prolonged uterine hæmorrhage was a feature common to the 15 patients under consideration Two of them had uterine fibromyomata and one had an ovarian cyst while the remaining 12 did not show any abnormalities on vaginal examination Histological examination of endometrial tissue after the cessation of bleeding revealed follicular phase in six early luteal phase in two luteal phase in three and menopausal endometrium in one case In three cases, curettage was not performed following EACA treatment

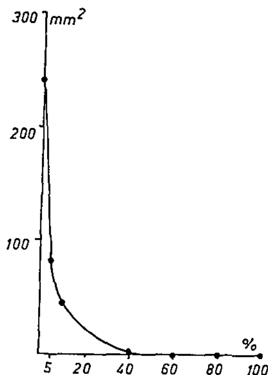


Fig 6 The inhibitory effect of EACA on the plasminogen activator of menstrual blood For details, see text – Abscissa and ordinate as in Figure 5

All the patients were given EACA on the first or second day after the onset of bleeding Bleeding ceased completely after treatment for 24 hours in 13 of the 15 patients, a phase at which the bleeding had previously been very profuse In one patient (Case 7), the intensity of the bleeding was reduced, but complete cessation was not achieved in spite of very intensive therapy Hysterectomy was then performed In another patient (Case 11), the treatment had to be discontinued after only two doses of 30 ml EACA because serious side effects developed At this time, the bleeding had become greatly reduced

The side effects were relatively mild except for those observed in Case 11, and in the majority of the patients were manifested by headache, dizziness, nausea and diarrhœa However, these side effects were not so severe that it was necessary to discontinue the

treatment, and the symptoms disappeared immediately after the termination of treatment

All the patients revealed normal coagulation values in the peripheral blood before the commencement of treatment Thus, the thromboplastin generation was normal, evidencing a normal concentration of the plasma thromboplastin components factor VIII (anti hæmophilic globulin A), factor IX (anti hæmophilic globulin B), factor XI (plasma thromboplastin antecedent) and factor XII (Hageman factor) The concentrations of the factors II–VII (prothrombin proconvertin) and V (proaccelerin) were also within normal limits, and the concentration of factor I (fibrinogen) was normal These last observations are confirmed by the finding of normal prothrombin times One patient revealed a slight increase in the concentration of plasminogen activator, while the others did not show any signs of increased fibrinolytic activity

A number of previous studies have shown that during uterine hæmorrhage especially menstrual periods, an increase occurs in the fibrinolytic activity of the peripheral blood (Willson and Munnel 1946 Marx and Rovatti, 1952, Dausset Bergerot Blondel and Colin, 1957) Other authors have been unable to confirm this observation (Macfarlane and Biggs, 1946) However no unquestionable methods are as yet available for a quantitative determination of the fibrinolytic components of the blood because it has not been possible to separate the active and inhibitory components The discrepancy just mentioned should presumably be viewed against this background In the analyses reported in this paper, no attempts were made to isolate the fibrinolytically active components from their inhibitors

The studies reported here thus show that disturbances in the coagulation of the peripheral blood cannot explain profuse vaginal hæmorrhage although it must be emphasised that investigations concerning the role of the platelets were not performed

At the termination of the treatment and the cessation of the bleeding the coagulation values were found to be unchanged Although the methods used are presumably unable to reflect minute changes in the concentration of the coagulation components it must be assumed that EACA does not exert an influence on these under normal conditions The increased fibrinolytic

activity which was observed before the treatment in one patient disappeared, presumably as a consequence of the treatment. The fibrin plate method which was used in the present study does not allow of determination of the weak fibrinolytic activity which must be assumed to be present in the blood even under normal conditions. Accordingly, the possibility of an inhibition of this activity during EACA therapy cannot be excluded.

The reduced concentrations of the factors II–VII and V in the vaginal blood before the institution of treatment correlated with the absence of thromboplastin generation and the increased thromboplastic activity which was observed in several cases suggest that *intra-uterine coagulation occurred, with consumption* of the coagulation factors. The results of the determinations of the prothrombin times point in the same direction. Tissue thromboplastin from the endometrium must be supposed to play a part in this process. The fibrin formed has then been dissolved by the plasminogen activator liberated from the endometrium through an activation of the plasminogen present in the fibrin.

The ability of EACA to arrest uterine bleeding must be assumed to be due to an inhibition of the local fibrinolytic process. The inhibitory effect of EACA on the plasminogen activator *from the endometrium and on the fibrinolytic activity of menstrual* blood provides evidence in support of this assumption. The result of such an inhibition will be that intra uterine coagulation will proceed unimpeded, and that the clot formed may have a hæmostatic effect. Further evidence in support of this view is provided by the observation made in case 13 in which hysterectomy was performed. The operation revealed a large submucous fibromyoma covered by a massive, adherent layer of fibrin.

As already mentioned, the anti fibrinolytic effect of EACA is due to an inhibition of the conversion of the plasminogen into the active enzyme, plasmin, and possibly also to an anti plasmin effect. As all the samples studied revealed plasminogen activator in the endometrium after the termination of treatment, the effect cannot be due to destruction of this activator.

In spite of intensive therapy, it proved impossible to arrest the bleeding in case 7, although it was considerably reduced. The content of plasminogen activator in the endometrium from this

patient was higher than in any of the other samples of endometrial tissue studied It is thus possible that the amount of EACA administered was unable to inhibit the intra uterine fibrinolysis because of the high activator concentration

It is generally assumed that morphological changes play a greater part in the arrest of these hæmorrhages than enzymatic processes (Beller, 1957) Thus, during normal menstruation, histological examination reveals a mixture of cellular degeneration and regeneration of the mucosa Only when the regeneration is complete does the bleeding stop It appears that six of the endometrial samples studied were in the follicular phase after the cessation of the bleeding It is possible that the uterine mucosa once the bleeding has stopped under EACA therapy, is capable of regenerating beneath the layer of fibrin which has formed resulting in permanent hæmostasis

Although EACA has proved to be effective in the treatment of uterine hæmorrhages, there are reasons to warn against an uncritical use of the drug against bleeding of unknown ætiology Although the mechanism of bleeding in patients with uterine cancer must be presumed to differ from that described here, so that it is doubtful that EACA would be effective in such cases, the presence of cancer must be definitely excluded before EACA therapy is instituted Moreover, at the present time, EACA should not be used routinely in the treatment of menometrorrhagia, even if malignancy can be ruled out Cases are on record in which treatment with EACA after prostatectomy was complicated by thrombosis presumably as a consequence of an inhibition of an increased fibrinolysis directed against such thrombosis (Nacye, 1962) Finally it is as yet unknown what consequences may follow an inhibition of the normal fibrinolytic activity of the organism In the presen study only the immediate action on profuse vaginal hæmorrhage was analysed and no attempts were made to assess the long term effects of the drug

It is known from many previous investigations that EACA is effective against hæmorrhagic diatheses caused by an activation of the fibrinolytic enzyme system of the circulating blood (for references see Nilsson Bjorkman and Andersson 1961) The present study shows that EACA is also effective in the treatment

of local coagulation disturbances It must be presumed that this will prove to be of importance in certain local fibrinolytic processes which are known to occur in relation to certain surgical measures The hæmorrhage from the prostatic capsule after prostatectomy is presumably due to a fibrinolytic process, which is activated by local liberation of plasminogen activator from the tissue which has been injured by the operation (Rasmussen and Albrechtsen, 1960, Ladehoff and Rasmussen, 1961) Similar conditions may obtain in local oozing of blood after operations, *for example*, on the lungs or the thyreoid gland *It* is reasonable to assume that EACA may prove to be effective in the treatment of such conditions (Sack, Spaet, Gentile and *Hudson, 1961*)

SUMMARY

Oral administration of epsilon aminocaproic acid was used in the treatment of 15 patients with profuse uterine hæmorrhage In 13 of these, the bleeding ceased after treatment for 24 hours, while the bleeding continued in one, although with diminished intensity In one patient the treatment had to be discontinued because of serious side effects

Studies on the peripheral blood showed normal coagulation values both before the institution of the therapy and after its termination

Studies on vaginal blood before the commencement of treatment seemed to show that intra uterine coagulation occurred *during the bleeding, and that the formed clot was dissolved by a* vigorous fibrinolytic process referable to liberation of plasminogen activator from the endometrium

In vitro experiments revealed that both the plasminogen activator of the endometrium and that present in menstrual blood can be inhibited by epsilon-aminocaproic acid

It must therefore be assumed that the effect of the drug on uterine bleeding is due to inhibition of the local fibrinolytic process occurring in the uterus during the bleeding

The authors warn against the use of epsilon aminocaproic acid

when malignancy cannot be excluded and advise against its use at least at the present time, in symptomatic treatment even when malignant disease is absent

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EXPERIMENTAL AND CLINICAL STUDIES ON THE FLUOROBIOLOGY OF THE CERVIX[1]

I The Fluorescence of Rodents Smears Stained in Vivo by Diaminoacridines

BY

M. SHERIF[2]

MB BCH DGO DS MCH

Acridine was first isolated from the crude anthracene fraction of coal tar by Groebe and Caro in 1871 Seven years later its structural formula $C_{13}H_9N$ was established by Bernthsen

Medical interest in its substitutes started with the discovery, in 1913 of the antibacterial action of acriflavine and proflavine and was further increased with the synthesis of atebrin in 1930, the first antimalarial to rival quinine in its activity

With accelerated pace of investigation, many of the biologic and therapeutic properties of the acridine series were established These were attributed to their physicochemical properties mainly to the charged nature of the parent acridine molecule and its state of electronic excitation (Albert 1951) Diaminoacridines as a class have been used as antibacterials antimalarials dye stuffs and cancer therapeutic agents (Lettre 1941 Martin 1944 Lewis 1948 Marsh and Simpson 1927) Their intense fluorescence on long ultraviolet and blue light excitation

[1] The studies are part of A New Cancer Test awarded the Edgar Gentilli's prize for the year 1962 and the year 1963 by the Royal College of Obstetricians and Gynæcologists

[2] Lecturer Alexandria University Egypt U A R

rendered them highly suitable for fluoranalytic studies, in titrational determinations, fluorohistology (Armstrong, 1956), to detect cellular viability in botany, in zoology and in radiobiology (Krebs and Gierlach, 1951, Strugger *et al*, 1953) Recently, acridine orange (3–6 bis-Dimethylamino acridine), was recommended and utilized in cytological techniques as a differential cancer stain (Bertalanffy, Masin and Masin, 1958)

A property of diaminoacridines, hitherto uninvestigated, is their unique affinity among all basic dyes to interact with nucleic acids of the living cell, of both normal and malignant tissues, and to exhibit, on proper excitation, different fluorescence spectra specific for each of them (Sherif, 1963) To confirm these observations, the presented study was conducted to verify at the cellular level

1 The affinity of diaminoacridines to nucleic acids of the cervical epithelia of rodents *in vivo*
2 The fluorescence of the stained cells, and its variations with physiologic (non-neoplastic) processes

Materials and Methods

The diaminoacridines* investigated were

3–6 diamino-acridine sulphate (Proflavine Sulphate)
3–6 diamino acridine hydrochloride (Proflavine Hydrochloride)
3–6 bis-Dimethylamino acridine (Acridine Orange)
3–6 diamino-N methyl acridinium chloride (Trypaflavine)
3–6 diamino-10 methyl acridinium chloride and 3–6 diamino acridine (Acriflavine)
3 amino 6 dimethylamino-2 methyl acridinium hydrochloride (Coriphosphine O)
6 9 diamino-2-ethoxy-acridine lactate (Rivanol)

Animals used were female rabbits (20), rats (30), and mice (40) Aqueous fresh solutions of the dyes were administered in

* Kindly supplied by the Department of Medical Chemistry Australian National University, Australia The British Drug House London E I Du Pont De Nemours & Co, U S A, Schmid & Co Stuttgart Germany and Hopkins & Williams Ltd Essex England

single doses of 10 mg/kg body weight, by different routes (intraperitoneal subcutaneous, intramuscular and for the rabbits, orally and through the ear vein) Cervical smears were collected at different intervals (few minutes up to 48 hours) after administration of dyes, spread on glass slide, without fixation, and immediately examined after moistening with a drop of freshly prepared phosphate buffer (pH 6 2)

The microscope used was a Leitz Ortholux III, with built in eye piece 4 x for photomicrography, dark field condenser D 0 80 for dry objectives 10–40 x up to numerical aperture 0 65, and D 1 20 A for immersion lens 100 x

The excitation source was a Leitz fluorescence lamp, with Philips CS 150 watt mercury high pressure lamp, and a filter BG 12 for the blue spectral range (4040–4360 A)

Photographs were taken with the automatic microscope camera Orthomat Leitz which has a built in exposure metere for fluorescense

Automatic exposure time varied from 50 seconds to 2 minutes High speed Ektachrome Kodak films were used

Special variations

1 Ten of each species of the test animals were given repeated injections of 5 μ œstradiol subcutaneously in 0 5 cc of sesame oil before and during the experiment
2 To study the effect of cellular devitalisation electric or thermal cauterization of the endocervical canal and ectocervix of ten anæsthetized animals was performed before vital staining

Results

The results are summarized as follows

1 As judged by the fluorescence all tested diaminoacridines stained the different cervical cells in vivo, irrespective of the route of administration
- Diaminoacridines with substitution at the 3 and 6 positions exhibited the strongest affinity with minimal variations in the time lapse between administration and fluorescence, its

Provided by The Leitz Swedish Agency Stockholm

intensity, its peak and its duration

3 Individual nuclei exhibited *strong localised fluorescence which* corresponded to their particular chromatin pattern The cyto plasm of most cells, however, exhibited a diffuse, very faint fluorescence with no tendency to localisation Some cells did not exhibit cytoplasmic fluorescence *(Plate I)*

4 With the exception of devitalised cells, all cells exhibited green fluorescence, with minor variations in colour of nuclei related to the stratum from which the cells were derived

5 Nuclei of the cells obtained from œstrogen-treated animals showed definite mitotic activity due to hyperœstronæmia, yet the fluorescence was the same, in colour, and practically the same in intensity No variations were noticed in the cyto-plasmic fluorescence (Plate II)

6 Devitalised cells exhibited red cytoplasmic fluorescence (Plate III) Acridine orange was the most sensitive dye to reveal such a change and was, indeed, almost specific to indicate devitalisation

Discussion

As first pointed out by Miescher (1897), nucleic acids exist *in the living cells in a salt-like combination with the basic pro* teins Evidences on the integrity of the nucleoprotein complex have been recently obtained by X-ray diffraction techniques (Feughelman *et al*, 1955) Where both acids and proteins are together, their linkage makes them unstainable (Hammarsten and Teorell, 1928) This is due to the effective combination of the negatively charged acidic phosphate groups and the posi tively charged basic polypeptide groups Nucleic acid staining with basic dyes, in cytological and histological preparations, is achieved after cellular death due to severance of the nucleopro tein complex and consequent accessibility of the phosphoric acid groups to the dyes' kations (Michaelis, 1947) Diamino-acridines have a unique ability to stain the living cells with a distribution *corresponding to that of* D N A *and* R N A (De Bruyn *et al*, 1950, 1953, Meisel, 1951, Sherif, 1963)

This study, the first reported *at the cellular level,* proves the

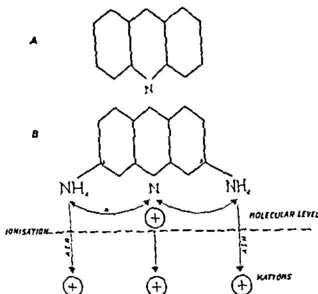


Fig 1 A The skeleton of acridine – B Diaminoacridine molecule with substitution at the 3 and 6 positions R = Resonance between amino groups and ionised ring nitrogen A I R = Additional ionic resonance

ability of diaminoacridines to combine with nucleic acids of the living cells of the cervix of rodents

The mechanism of the interaction has been discussed in detail by the author (Sherif, 1963) Presumably the combination is electrostatic one directed and modified by the molecular architecture of diaminoacridines and nucleic acids

The acridine molecule possesses a totally planar structure with three regular hexagons and a ring nitrogen atom at the tenth position (Fig 1 A) The charged state of the molecule evidenced by its high resonance energy and its intense fluorescence, is responsible for the remarkable ionisation of its substitutes, and their high basic strength Though the parent acridine molecule is a moderately strong base which ionises to the extent of 1% only at pH 7 3 and temperature 37 its relative basic strength is markedly increased with the insertion of double amino groups The effect however would be essentially dependent on the sub-

intensity, its peak and its duration

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Plate I

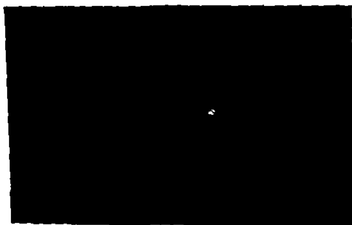


Plate II



Plate III

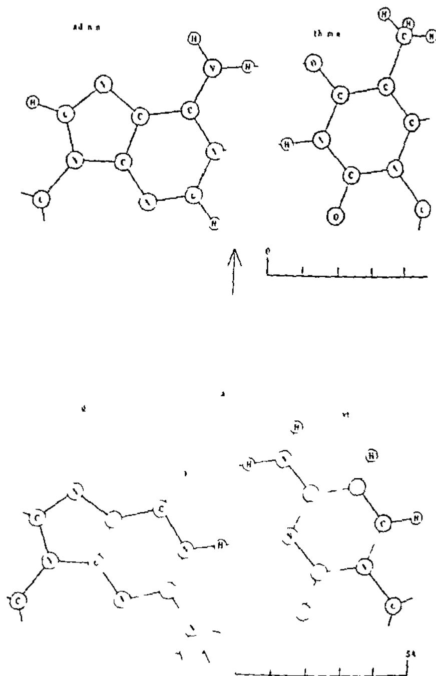
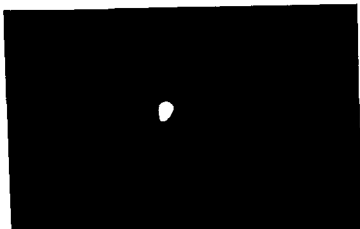


Fig 2 Pairing of bases of nucleic acid molecule (D N A) Hydrogen bonds are shown dotted (Crick and Watson 1954)


Plate I

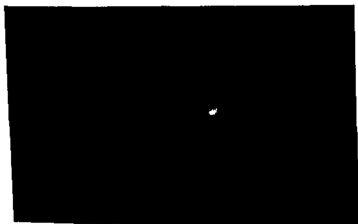
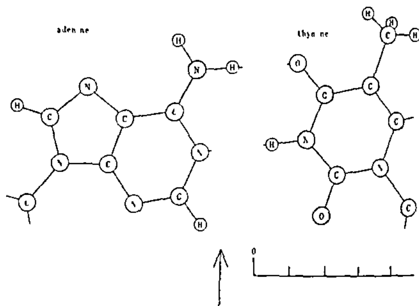

Plate II


Plate III



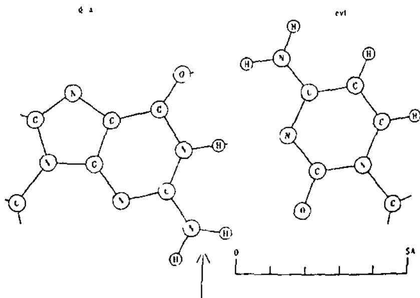


Fig 2 Pairing of bases of nucleic acid molecule (D N A) Hydrogen bonds are shown dotted (Crick and Watson 1954)

situon sites Maximum basic strength is achieved when the two amino groups are inserted at the 3 and 6 positions, where they would resonate with the ionised nitrogen atom, and would ex hibit the phenomenon of additional ionic resonance (Fig 1 B) This occurs when a base is found to be stronger than it may otherwise have been through the extra resonance aquired during passing from a molecule to ion (Albert, 1951) The high basic strength of all 3 6 diaminoacridines renders their molecules highly ionisable to kations at pH 7 3, and Temp 37 Each kation is planar in shape with every atom lying at the same horizontal plane This flatness enables it to strike any appropriate flat recep tor with which it is brought in conctact and establish a number of van der Waals bonds with it (Albert, 1951)

In the present state of knowledge (Sherif, 1963) the most likely vital receptor for the acridine kations on the nucleic acid molecule seems to be the nucleotide leaves where the combina tion can be established through competition of the kations with the hydrogen ions linking the nitrogen bases for the position of the weakly acidic groups of the bases (Fig 2)

With such a mechanism, the selective affinity of diamino acridines to different nucleic acids of the living cells *can be attri* buted to one or more of the following factors

1 Difference in molecular architecture of D N A, intranuclear R N A and cytoplasmic R N A

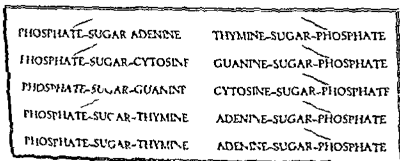


Fig 3 Diagrammatic representation of part of a hypothetical polynucleotide chain in nucleic acid (*D N A*) to demonstrate irregularity of the sequence of bases

lach, 1951] Similar results have been obtained with human sperms, and animal tissues (Schümmelfeder 1950, van Duijn, 1954) Cellular damage is associated with dissociation of the nucleoprotein complex, and the behaviour of diaminoacridines towards cytoplasmic R N A of the devitalised cells would be consequently similar to their behaviour towards cells of histological preparations in vitro Fig 4 represents the distribution of nucleic acids in a cervical cell and the difference in the mode of interaction between diaminoacridines and each acid in the living and the devitalised cell

Conclusions

1 Diaminoacridines exhibit a strong affinity to interact *in vivo* with nucleic acids of epithelial cells of the cervix of the rodents

2 The interaction is directed by the chemical and electronic structure of the diaminoacridine molecule its steric arrangement high basic strength and large flat area

3 The *affinity* of the dyes is essentially selective to nucleic acids of different subcellular compartments It is marked for intra nuclear nucleic acids and almost absent for cytoplasmic R N A *Selectivity* is attributed to physicochemical heterogenicity of the acids

4 Physiological variations (hyperœstronæmia) are not followed by changes in the selective *affinity*

5 Devitalisation of the cells abolishes the selective affinity, conceivably through the induction of a dissociation change in the nucleoprotein complex

6 The intensity and colour of the fluorescence is dependent essentially on those considerations a uniform green fluorescence of moderate intensity is preceptible from all cells unchanged with physiological variations while red cytoplasmic fluorescence is perceptible only from devitalised cells stained with acridine orange

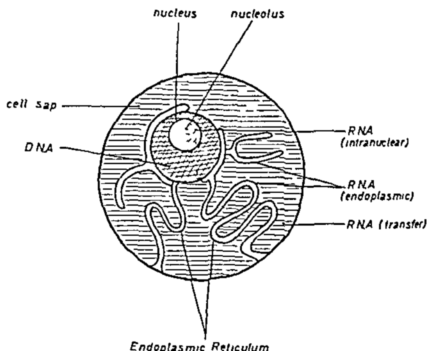


Fig 4 Distribution of nucleic acids in a cervical cell *In vivo*, diaminoacridines interact with intranuclear nucleic acids of the living cell and with intra nuclear and cytoplasmic nucleic acids of the devitalised cell

2 Variations in the molar proportions of bases in the three acids (Chargaff *et al*, 1950, Elson *et al*, 1955)

3 Irregularity of the sequence of bases on the phosphate sugar chains of the acids (Fig 3) (Smith and Markham, 1952)

Œstrogen administration to rodents leads to rapid and extensive synthesis of RNA in the uterine cells (Telfer, 1953) Lack of fluorescence of the cytoplasm of œstrogen stimulated cells proves that quantitative increase in cytoplasmic RNA, under physiological conditions, does not influence the selective affinity of diaminoacridines to various nucleic acids of the subcellular particulates

Variations of the fluorescence of acridine orange with changes in cellular vitality have been demonstrated in plant cells (Strugger, 1949) The staining effect of the dye on the protoplasm of Allium Cepa was found to depend on the degree of destruction by heat, mechanical injury, and gamma rays (Krebs and Gier-

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SUMMARY

The first report on vital staining of the cervical smears of rodents by diaminoacridines is presented The possible factors directing and modifying the interaction of the dyes and the nucleic acids of the cells are discussed

Further experimental and clinical work is in progress and it is hoped that with this reaction and with the application of an optic fluorescence unit to examine the human cervix* *in situ*, more could be known about the biochemical behaviour of the living cervical cells, in normal, and in neoplastic conditions

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* The Fluorescence Cervicoscope developed by J D Moller, Optic Works, Wedel, Hamburg

cells has been demonstrated in leukoplakia (Botella-Llusia, 1961), basal cell hyperplasia, and Hinselmans atypical epithelium (Berger, 1961), endocervical glandular hyperplasia, and endocervicitis (Herovici, 1960)

The identifying sign of the cancer cell stained in vitro by acridine orange (Bertalanffy *et al* 1958), namely the red cytoplasmic fluorescence, is also observed constantly in active cells of cervical erosions, secretory cells of the endocervix, basal cells of cervical dysplasia, and most cells associated with trichomonas and monilia infection (Bertalanffy *et al*, 1961)

This is due to the fact that the sign essentially reflects concentration changes of cytoplasmic R N A rather than a specific tumorogenic property of the cell A cancer cell is by no means the only cell which has a high content of cytoplasmic R N A for this substance is abundant in all proliferative and secretory cells engaged in active protein synthesis and in any other cell subjected to physiological or experimental factors that *modify* its biological activity in this particular direction (Caspersson, 1950 Brachet, 1957 Caspersson and Thorell 1941 Denucé 1952 Abolins 1952 Di Stefano, 1952, Oram, 1955 Telfer 1953, and others)

In vivo acridine orange in common with all the diaminoacridines interacts with nucleic acids This unique affinity among all basic dyes is characteristically selective towards nucleic acids of different subcellular compartments In the genital epithelia of rodents cytoplasmic R N A shows no tendency to interact with or to localize parenterally administrated acridine orange in contrast to intranuclear nucleic acids which show marked affinity for the dye (De Bruyn *et al* 1953 Sherif 1963) Physiological increase in nucleic acids is not associated with perceptible variations in the selective affinity of acridine orange to the acids and in the hyperoestrogenic cell abundant cytoplasmic R N A continues to resist the interaction of the dye and the cell exhibits no variations in the fluorescence on proper excitation (Sherif 1963) This has been explained by the difference in the molecular architecture of different nucleic acids within the same cell with subsequent modification of the interaction process (Sherif 1963) The study presented was conducted to

Sherif M Acta obst. et gynec scandinav 4 19 1963

From the Department of Obstetrics and Gynæcology, Sabbatsbergs Hospital, Karolinska Institutet (Professor A Ingelman Sundberg), Stockholm Sweden

EXPERIMENTAL AND CLINICAL STUDIES ON THE FLUOROBIOLOGY OF THE CERVIX

II Nucleic Acids' Variations in Early Stages of Induced Carcinogenesis

BY

M. SHERIF[1]

MB B CH D G O D S M.CH

Following the significant observations of Caspersson and Santesson (1942) on nucleic acids disturbances in epithelial tumours, much has been done to study their variations in experimental and spontaneous neoplasms (Stowell, 1946, Moberger, 1954, Leuchtenberger *et al*, 1954, Metais and Mendel, 1950, Mellors *et al*, 1952, Bader, 1953, Klein, 1951, Goldberg *et al*, 1950, Carnes *et al*, 1952, and others)

In neoplastic transformations of the human cervix, histochemical reports indicate an overall quantitative increase of DNA and RNA (Hopman, 1961, Herovici, 1960, Berger, 1961, and others), and this increase has been proved by ultraviolet cytophotometry (Mellors *et al*, 1952), nuclear weighing with interference microscopy and planimetry (Foraker, 1961), characterization of basic and acidic aminoacids by the pH signature technique (Foraker, 1961) and fluorescence cytology (Bertalanffy *et al*, 1958)

No specific relationship could be established, however, between the carcinogenetic process and the observations previously reported, since marked increase in the total acids of the cervical

[1] Lecturer, Alexandria University, Egypt, U A R

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3 Generally the spectral emission of the smears was in the green range

B Forty eight hours

1 Carcinogen crystals were evident in the cytoplasm, less brilliant than before, with no trace of the carcinogen in the nuclei

2 A large number of cells showed marked increase in the intensity of the fluorescence of their nuclei, especially at the centre This was evident in the squamous superficial cells, and to a less extent in many basal and parabasal cells Many cells showed yellow golden fluorescence of the cytoplasm starting at the outer border of the cell at one or more points The reaction of the nucleus was not, however, related to the reaction of the cytoplasm (Plates I and II)

3 Generally, the spectral emission for the smear was in the green range However, some cells showed cellular polychromasia

C Seventy two hours

1 Crystals were less evident than before, but could still be identified in the cytoplasm but not in the nucleus

2 Most of the cells showed intense fluorescence of the nuclei, both at the centre and at the periphery, with evident shift of the colour towards the orange

3 Most of the cells showed yellow golden cytoplasmic fluorescence of high intensity The changes were more marked in superficial squamous cells

4 Smears were polychromatic

D Ninety six hours

1 Carcinogen crystals were no longer identifiable

2 Nuclear and cytoplasmic changes were more pronounced

Discussion

Cytoplasmic R N A

Fluorescent derivatives of carcinogenic hydrocarbons are formed through chemical combination with proteins of the cells within

verify any possible change in the dye-acids interaction during the process of experimental carcinogenesis, to interpret any such change, and to correlate it with the stage of development of cervical malignancy The present report is concerned with the earliest observations obtained

Material and Methods

Animals used were 30 C3H female mice,* with average weight of 17 gms and approximate age of 10 weeks They were caged in groups of five, and given a stock diet

The carcinogen used was 20-methylcholanthrene dissolved in acetone, in a ratio of 1 100, and applied to the cervix of each anæsthetized animal

Smears were collected 24–48–72–96 hours following a single application Vital staining with acridine orange was accomplished by parenteral administration (intraperitoneal) of 10 mg/kg body weight of the dye three hours before the smears were obtained

All smears were examined immediately, and compared with control smears of untreated animals The technique for examination, the optical, and fluorescence requirements have been described in detail (Sherif, 1963)

Results

The results of the study were correlated with the time lapse between the application of the carcinogen and the cytological examination as follows

A Twenty four hours

1 Fluorescent 20-methylcholanthrene crystals were observed in the cytoplasm of the squamous cells but not in the nuclei, the crystals showed marked brilliant intensity

2 No change in the fluorescence of the nucleonucleolar mass, *nor in* the faint fluorescence of the cytoplasm was observed

* Obtained from the Tumour Biology Institute Stockholm

Brachet (1957) to conclude that the cancer cells might contain a special type of RNA, and its presence would lead to alterations in the mechanism of protein synthesis If such abnormal RNA is proved to exist, the observations reported would date it to early interaction with the carcinogen

That the change in the cytoplasmic RNA is not only qualitative is evidenced by the change in the spectral range of the emitted fluorescence High intensity of the fluorescence indicates maximal kation interaction and aggregation of the acridine molecules in the helices of the nucleic acids, and reflects a quantitative increase in the acid molecules This is supported by previous reports concerning the increase of cytoplasmic RNA as estimated by rœntgen absorption and ultraviolet spectrophotometry in mouse vaginal cells during early induced carcinogenesis (Moberger, 1954)

Intranuclear DNA and RNA

Though the carcinogen was not observed to interact with the nuclei, intranuclear nucleic acids showed a definite quantitative increase evidenced by the increased intensity of the nuclear fluorescence and its shift towards the orange range The increase was noticed in two distinct phases, the first was observed in cells that did not present cytoplasmic interaction and the second followed complete interaction of the carcinogen with cytoplasmic RNA In the first phase the increase was moderate, in the second it was marked, both judged by the fluorescence of the nuclei Presumably the first phase represents an initial host reaction of the nucleonucleolar machinery to the carcinogen followed in the second phase by its reactive hyperfunction to correct the disturbed protein metabolism of the cell induced through the drastic change in the molecular architecture of the cytoplasmic RNA

Conclusions

1 In induced cervical carcinogenesis 20 methylcholanthrene interacts with the cytoplasm of the cervicovaginal cells conceivably with the protein moiety of the cytoplasmic ribo

a few hours of painting Failure to detect them in the nuclei indicates that the initial binding is established within the cytoplasm Supporting evidence is obtained in the findings of Zamenhof *et al* (1954), that methylcholanthrene does not influence the transforming activity of Hæmophilus Influenza Desoxyribonucleic acid, though Ultraviolet light and nitrogen mustard activate it

Cell fractionation studies proved that carcinogens are attached to nucleoproteins particulates and to soluble protein but not to nucleic acids (Wiest and Heidelberger, 1953) The development of cytoplasmic fluorescence in the cells interacted with the carcinogen in this study proves the accessibility of the R N A to the diaminoacridine kations and confirms the results obtained by cell fractionation Since the integrated ribonucleoprotein molecule of the living cell is proved to resist the interaction with the acridine kation (Sherif, 1963, De Bruyn *et al*, 1953) the observations reported would point to either disaggregation of the ribonucleoprotein complex and its subsequent denaturation, with the release of the nucleic acid under the influence of the carcinogenic agent, or to change *in the molecular architecture of* R N A in the intact complex which would favour electrostatically and sterically its interaction with the dyes kations Diffusion of intranuclear R N A to the cytoplasm is improbable, since the cytoplasmic fluorescence was observed initially at the outer side of the cell

Cytoplasmic R N A is the template for protein synthesis, and in the cancer cell, the general composition of the proteins remains unchanged, but there would be changes in the internal configuration of the protein molecule, in its folding specificity (Rondoni, 1955, Brachet, 1957) R N A isolated from leukæmic blood is abnormal in composition particularly in its uracil content in comparison with normal blood Further, urethan, a very active carcinogen, modifies the metabolism of purines and pyrimidines, and inhibits thymine synthesis (Boyland and Koller, 1954) Strong evidence for alteration of R N A in carcinogenesis is reported by Ledoux, 1955 who showed that the ratio of different bases of the *ribonucleoprotein complex are significantly modified* in ascitic tumour cells during ribonuclease therapy This led

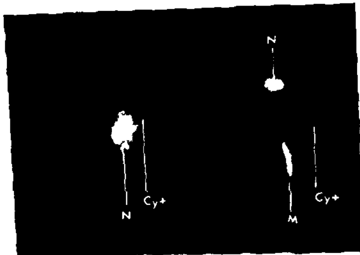


Plate I

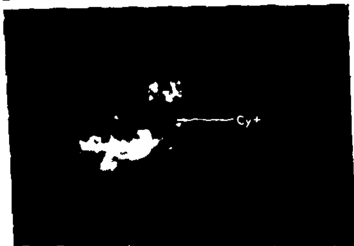


Plate II

Cyt Cytoplasm

N Nucleus

M Me 20 methyl cholanthrene crystals

nucleate, with consequent qualitative molecular changes in cytoplasmic R N A Stained *in vivo* with acridine orange, these cells would exhibit golden-yellow cytoplasmic fluorescence

2 Intranuclear nucleic acids show quantitative increase induced by the carcinogen but not due to direct interaction with it

SUMMARY

The first results of a study conducted to verify variations in nucleic acids in the living cells during induced cervical carcinogenesis are presented The selective affinity of acridine orange to interact with different nucleic acids in vivo, the fluorescence of the resulting complexes, and that of the carcinogenic hydrocarbon derivatives were utilized to observe the earliest changes Qualitative and quantitative variations in the acids consequent to the action of the carcinogen are described and discussed

Acknowledgments

The author is indebted to the Council of the Royal College of Obstetricians and Gynæcologists for the two successive awards, to Professor A Ingelman-Sundberg, M D, for his unfailing help and encouragement and to Docent M Furuhjelm, M D, for the permission to carry out the experiments at the Hormone Laboratorium

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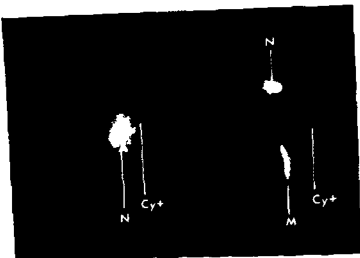


Plate I

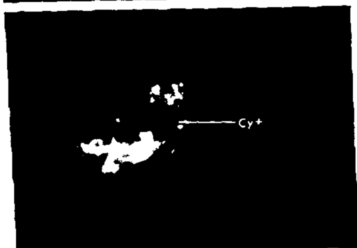


Plate II

Cyt Cytoplasm

N Nucleus

M Me 20 methyl cholanthrene crystals

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Tervilä Leo Acta obst et gynec scandinav 4 –00 1963

From the First and Second Departments of Obstetrics and Gynæcology (Professor Aarno Turunen and Professor Paavo Vara) and from the Gynæcologic Section of the Department of Radiation Therapy (Professor Veikko Kahanpaa), Central University Hospital, Helsinki, Finland

CARCINOMA OF THE CERVICAL STUMP

BY

LEO TERVILA

The term carcinoma of the cervical stump is commonly used for carcinoma developing in the stump after such a great length of time that it may be considered to have had its onset subsequent to the primary operation One year is usually considered an adequate interval, although, according to some authors two, or even three years are required in order to confirm this diagnosis

Carcinoma of the cervix is relatively rare following supra vaginal amputation of the uterus, but the incidence is high enough to justify its being held in mind in the choice of the sur gical procedure for the removal of uterine myomas for example Reports on the incidence of this form of carcinoma vary, as is seen in Table I, in which the minimum period of observation was generally 2 years

The length of time after which the follow up examination was made has of course a definite effect on the incidence A true picture of the situation is obtained only after death of the patient, giving a lifetime period of observation

Statistics from the Departments of Obstetrics and Gynæcology and the Department of Radiation Therapy of the Central Uni versity Hospital, Helsinki, on carcinoma of the cervical stump have been published twice 29 cases in 1945 by Vara, and 41 cases in 1953 by Turtola The reason why it now has been considered necessary to analyze the cases occurring during the

Table I

Author	Cases Followed-Up	Stump Carcinoma	Follow Up Period
	No		Yrs.
Albrecht		0 32	1
Berger	483	1 02	2
Fahndrich	17 139	0 39	2
v Graff	1 774	0 7	2
Henriksen	6 550	0 4	2
Lamp	21 516	0 525	2
Lefevbre & Gouzi	22 165	0 5	2
Martius		0 3	2
Meigs	2 523	1 6	2
		0 7	1
Pearse	810	1 0	2
Pedkina	58	1 7	2
Saegesser	620	1 9	2
Sander	20 062	0 8	2
Young	16 000	0 56	2

past few years is that progress in medical science may have changed the principles according to which conclusions were drawn in the earlier reports

The present series of cases were treated in the Department of Obstetrics and Gynæcology in 1943–57, and in the Department of Radiation Therapy in 1952–57 A total of 2 833 patients with carcinoma of the cervix were treated in the hospital in these periods They included 55 cases (1 9 per cent) of carcinoma of the cervical stump the onset of which had been over one year after the primary operation In 5 cases the disease had begun more than one year but less than two years after subtotal hysterectomy Three cases were excluded in which the carcinoma was diagnosed before one year had elapsed These figures indicate that the cervix had been examined preoperatively more carefully than previously since in Varas series 3 cases out of 29 were diagnosed during the first postoperative year and in Turtolas series 11

of 42 cases Compared also with series published in recent years, the present incidence is relatively low (follow up time 2 years) Ullery (1958), 24 of 82 cases, Decker (1957), 14 of 98 cases, Redkina (1959), 6 of 13 cases, and Fanghänel (1959), 1 of 17 cases

The incidence of carcinoma of the cervical stump calculated from all carcinomas of the cervix varies in different hospitals, being according to the *surveys by Turtola (1953) and Berger* (1960) in the range 0 5–8 3 per cent In the series of Vara (1945) it was 1 27 per cent, and in that of Turtola (1953) 1 5 per cent Thus the incidence appears to have increased slightly, as has been assumed also by a number of other investigators (*Stoekel, 1947, Koch, 1947, Fricke, 1958, Lachmann, 1950*)

The mean age of patients in the present series was 52 years, the youngest patient being 35 and the oldest 73 The mean ages reported in the literature are approximately the same (Ullery, 1958, *Decker, 1957, Fricke, 1958, Albrecht, 1953*)

Distributed by age groups there were 3 patients under 40, 21 aged 40–49, 21 aged 50–59, and 10 over 60 years When these are combined with the statistics collected by Vara and Turtola from the same hospital, making a total of 125 cases, the age distribution is as follows Under 40 years, 6 per cent (8 cases), 40–49 years, 35 per cent (43 cases), 50–59 years, 40 per cent (50 cases), and over 60 years, 19 per cent (24 cases) Compared with the general age distribution of carcinoma of the cervix (Krokfors, 1960) there is evident a definite shift to the older groups, and the youngest group particularly, is very small This observation is fully in agreement with the statement that carcinoma of the cervix occurs 5–10 years earlier than carcinoma of the *cervical stump (Berger, 1960)*

The series contained 44 women who had had deliveries and 8 (18 per cent) nullipare No information on the parity of 3 patients was available Twelve patients had had one delivery 14 patients 2, 9 patients 3 3 patients 4 and 6 patients over 4 *deliveries* Including the data given by Vara (Turtola did not give this information for his series), the parity distribution is as seen in Table II Compared with the general parity distribution

Table II

Indication	Nulli Paræ	I Paræ	II Paræ	III Paræ	IV Paræ	Over IV Paræ	No Inform	Total Number
Vara	9	7	5	1	1	6		29
Present Series	8	12	14	9	3	6	3	55
Total	17	19	19	10	4	12	3	84

of patients with carcinoma of the cervix (Krokfors, 1960), these clearly are relatively higher for nulliparæ and I and II paræ and lower for multiparæ A similar observation has been published earlier (Decker, 1957) Naturally the amputation of the uterus contributes to some extent to this low parity figure, but generally the operation was done at such a late age that its effect cannot be very great The indication for subtotal hyster ectomy as for example myomas and chronic inflammations, would have lowered fertility earlier in many cases

The mean age of the patients at the time of the primary opera tion was 42 years, there being as many as 24 patients aged 40 years or less in whom a conservative operation was justified because of age This age however, is quite high in comparison to statistics from the United States (Decker 1957) In Finland the effort is to save the patient where possible, from invalidating operations particularly before the age of 40 In 23 of the 55 cases in the present series one or both ovaries had been left in addition to the stump

The time interval between operation and diagnosis of the carcinoma was on the average 9 5 years Distributed into three groups the post operative interval was 1–3 years in 13 cases, 4–5 years in 6 cases and over 6 years in 35 cases in one case it was unknown It therefore seems as a number of authors have previously observed that as long as one year after the primary operation cases are seen in which it is probable that the carci noma was already present at the time of operation but developed so slowly that the symptoms did not become manifest until over one year later Vara s figures for the same chronological groups were 35 per cent 23 per cent and 42 per cent and were notably more evenly distributed than the present figures (24 per cent,

11 per cent, 65 per cent) A shift towards longer intervals is observable – presumably a sign of more thorough examination of the cervix

The indications for subtotal hysterectomy were stated in 47 cases uterine myoma in 27 cases, complications at delivery in 3 cases, metrorrhagia in 4 cases, various benign ovarian tumours in 8 cases, chronic infection in 2 cases, endometriosis in one case, oligomenorrhœa in one case, and ovarian carcinoma in one case

It is very difficult subsequently to express an opinion why total hysterectomy was not performed If the age of the patient being 40 years or less is accepted as the reason, there remain, after exclusion of the above mentioned 24 cases and 1 case in which information was lacking, 30 patients whose case histories have been subjected to analysis in the effort to clarify this point It was observed that one patient had rather severe cardiac insufficiency, one had moderately severe asthma, one had pulmonary tuberculosis at the time of the operation, and four an elevated blood pressure (160/120–240/140), two of the last mentioned also being obese The other patients had no particular medical contraindications for radical operation Twelve of the operations had been performed by surgeons in hospitals in which there was no gynæcologist, and 5 in small rural hospitals, where surgical facilities were probably not very good There remain only 16 cases in which no possible reason can be found for the conservative operation

The symptoms that brought the patients to the physician were those usually seen in cases of carcinoma of the cervix 50, or nearly all the patients, had irregular bleeding, 2 had pain, and the remaining patients discharge and loss of weight Fifteen cases were diagnosed within one month of the onset of symptoms, 36 cases over one month but less than one year after the first symptoms, and 3 cases after more than one year In 20 patients there was a tumour of the cervix, in 28 patients erosion at this site, while 4 patients showed no changes In severity 21 cases were grade I, 25 cases grade II, and 6 cases grade III

The histological diagnosis was stated in 36 cases squamous epithelial carcinoma in 29 cases, adenomatous carcinoma in 4 cases, and solid carcinoma in 3 cases

The treatment in 49 cases was irradiation alone in 5 cases combined irradiation and surgery, an in 1 case surgery alone The non operated patients received an average of 6413 mg hrs Ra or Co^{60} and additionally 7509 r rœntgen therapy The operation was excision of the cervical stump, these patients were addition ally given an average of 4449 mg hrs Ra or Co^{60} and 8269 r rœntgen therapy

Therapeutic complications were anæmia in 4 patients, leuko penia in 9, bladder damage in 3 rectal damage in 6, bladder and rectal damage in 3, and additionally skin lesions in 2 patients

Five years later 34 of the 55 patients were living The cause of death of 10 patients was confirmed at autopsy 8 died of car cinoma, one had a diagnosis of cerebral hæmorrhage and one of degeneration of the heart muscle The mortality rate thus was 38 per cent which is considerably lower than those of Vara (77 per cent) and Turtola (73 per cent) The earlier arrival of the patients for treatment definitely contributed to the im proved result, for comparison of the severity of the disease in the three investigations shows unexpectedly great differences

Investigation	Grade I	Grade II	Grade III	Grade IV	Grades III IV
Vara	12%	8%	38%	15%	27%
Turtola	25%	32%	29%	14%	
Present series	40%	48%	12%	–	

The benefit of early arrival is evident also in the distribution of the 32 surviving patients whose grade of disease is known grade I 15 grade II 16 grade II one patient

The literature usually reports fairly high mortality rates of 64–72 per cent (Ullery 1958 Nielsen 1937 Gagneten, 1960) and even 85 per cent (Blomfield 1959) This confirms the generally stated opinion that the prognosis of carcinoma of the cervical stump is poorer than that of the ordinary carcinoma of the cervix However Fricke and Decker (1958) have observed progress similar to that presented here They have published two series of cases of stump carcinoma from 1915–30 and 1940–49 and observed a drop in the mortality from 73 7 per cent

to 32 4 per cent Grades III and IV carcinomas were also much less frequent in the latter series

Discussion

Since the publication at the end of the last century of the first report of a carcinoma developing in a cervical stump, problems connected with this disease have been analysed in numerous reports The reason for this is that the disease can be avoided by the performance of total hysterectomy In choosing which of the two operations should be used in a case, consideration must of course be given to how much greater is the risk of a total than of a subtotal hysterectomy, to the probability of a carcinoma developing in the cervical stump, and to the mortality in stump carcinoma

Operative mortality has with time declined from year to year, thanks to improvement in the surgical and anæsthetic techniques the introduction of antibiotics, and increased knowledge of fluid and electrolyte balances In the Second Department of Obstetrics and Gynæcology of the Central University Hospital the mortality in 1935–48 was 1 11 per cent in subtotal hysterectomy, and 3 54 per cent in total hysterectomy (Vara, 1951) In the same hospital during the 3-year period 1949–51 the immediate mortality in 419 cases of subtotal hysterectomy was 1 67 per cent and in 122 cases of total hysterectomy 4 09 per cent (Eklof-Slangus) However, in the 9-year period 1952–60, during which the variations in the *annual mortality rates was not statistically significant* in either group, the mortality in 1151 subtotal hysterectomy cases was 6, or 0 52 per cent (± 0 16 per cent) and in 1257 total hysterectomy cases was 13, or 1 09 per cent (± 0 29 per cent) The difference between these figures is at the borderline of almost significant The probability of the difference is 94 6 per cent when the question is posed Is subtotal hysterectomy a safer procedure than total hysterectomy? It is well to note the similar trend of the difference in the above two series from successive periods of different length Since a statistically significant difference cannot be confirmed in this manner, the series from 1952–60 from the same investigation is given below after exclusion of all

cases of cancer There were 1065 subtotal hysterectomies, with 6 deaths (0 56 per cent) and 926 total hysterectomies with 10 deaths (1 01 per cent) This calculation makes the significance of the difference slightly lower still If we consider the group in which the operation was performed for myomas, we obtain a group that is as homogeneous as possible from the point of gynæcological disease and which therefore permits comparison of the risk involved in the two operations In 1949-60 a total of 1082 subtotal hysterectomies were performed and 7 patients, or 0 65 per cent died, of 718 patients undergoing total hysterectomy 7, or 0 97 per cent, died These two mortality rates show no significant difference and viewed against this background the very small difference shown above for the total series becomes even less significant

A similar development appears to have been seen elsewhere For example according to Meigs (1944) the primary mortality in the Massachusetts General Hospital was 4 4 per cent after total hysterectomy and 2 9 per cent after subtotal hysterectomy The difference accordingly was 1 5 per cent which was twice as high as the incidence of carcinoma of the cervical stump in the same hospital Nevertheless Meigs was already recommending the radical procedure as the primary operation in 1952

On the basis of large series in the literature the probability of development of malignant disease of the stump is c 0 5 per cent The 5 year mortality in the present series of 55 cases of carcinoma of the cervical stump was 38 per cent This figure was calculated from a rather small series but if it is used as a basis we find that the risk of death from carcinoma among patients undergoing subtotal hysterectomy is $\frac{0.5}{100} \times \frac{38}{100} \times 100 \approx$ 0 19 per cent Addition of the primary mortality of 0 52 per cent to this figure brings it up to 0 71 per cent This compares with the mortality of 1 03 per cent in total hysterectomy In view of the numerous inaccuracies and assumptions involved in the calculation of these figures the significance of the difference is open to question

The problem here considered cannot be solved merely by study of the mortality rates and it must be weighed separately in each

case with consideration to the patient's age, family relations and psyche, and the available medical possibilities In fairly young females and married women, in whom a normal sex life and an intact vaginal biology are desired, pelvic support maintained by the cervix and prevention of contraction of the vagina may be important points (Berger, 1960), even if cervicitis and erosion of the cervix remain as disturbing factors Naturally a benign tumour may also develop in the stump, calling for further operation (Kotsalo, 1957) Retention of the normal insertion of the utero-sacral ligaments as prophylaxis against prolapse is often to be taken into consideration in cases in which the pelvic tissues appear relaxed Careful operative technique can, of course, greatly reduce this risk even in the case of total hysterectomy, especially with the aid of the round ligaments The subjective feeling of invalidity that weighs down many patients after total hysterectomy is also to be held in mind

On the other hand, knowledge of a risk of cancer in the stump may in some cases be a disturbing fact If carcinoma does develop, its presence, although the disease in most cases is curable, may become such a psychic stress on some patients that it lowers their working capacity for many years

Since operative technique and the extent of surgery are evidently the conclusive factors in the primary mortality, they should be given as objective consideration as possible The possibility of excluding a latent malignant tumour by means of preoperative colposcopy and cytological examination of vaginal mucosa naturally reduces the risk taken in performing subtotal hysterectomy

SUMMARY

1 A series of 55 cases of carcinoma of the cervical stump treated in the Departments of Gynæcology and Obstetrics of the Central University Clinic, Helsinki, in 1943–57 and in the Department of Radiation Therapy of the same hospital in 1952–57 are analyzed with respect to the age and parity of patients and the severity, histological diagnosis, treatment, complications and prognosis of the disease The prognosis has greatly improved when

compared with that in previously published statistics, chiefly due to earlier arrival of patients for treatment Indications for the primary operation are also analyzed and the possibility of performing a total hysterectomy without risk to the patient is discussed

2 By comparison of statistical data the mortality risk was found ultimately to be approximately the same in the two operative procedures Surgical techniques have progressed so far that choice of the method of operation may be determined according to the individual case

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SOME FACTORS INFLUENCING THE RATE OF PREMATURITY

BY

ALF BACKMAN AND CARL ERIK UNNÉRUS

On the initiative of C E Raihä, a research team has studied for a number of years the problem of prematurity with particular reference to the hæmodynamic reasons for the birth of premature infants According to the results obtained from these studies the development of the fœtus is greatly dependent on the mother s hæmodynamic balance during pregnancy A simple standard of the mother s circulatory capacity is obtained by measuring her heart volume a small heart volume corresponds to a small cardiac output with the result that the circulation in the uterus and kid neys is more sensitive to an increased distribution of blood to other organs

In the present study attention was directed to the placenta the organ which acts as a sort of transformer between the maternal and fœtal circulation The work is a part of the programme of Raiha s research team

Series

The series collected from the Women s Clinics in Helsinki consisted of 704 deliveries 530 infants born at term and 174 born prematurely These figures reveal that there was some selec tion of material in the series owing to the nature of the problem, a greater proportion of premature infants than would be antici

pated, is included The incidence of premature birth in Helsinki is approximately 5 per cent, whereas in the present series the incidence is 24 per cent The overall incidence of prematurity in the hospital, from which this series is drawn, is 7 per cent

The following measurements were taken
Mother s height, cm,
Mother s weight in kg on the day after delivery,
Mother's heart volume It was measured rœntgenologically in a sitting position the day after delivery, expressed in cc, according to the method of Liljestrand *et al* (1939) as modified by Jonsell (1939) and developed further by Lind (1950) on the basis of the studies of Sjostrand (1953) and Kjellberg *et al* (1949)
Infant's birth weight, g,
Weight of placenta, g

Results

The series was analysed from different aspects and the following results were obtained

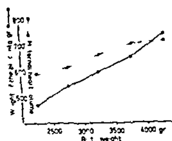
A A distinct correlation between the infant's birth weight, placental weight, and maternal heart volume is seen (see Table I and Fig 1)

Table I

Birth Weight	Mother s Heart Volume	Weight of Placenta
— 2499 g	584 ccm	470 g
2500 — 2999	609	546
3000 — 3499	653	596
3500 — 3999	699	650
4000 —	712	740

The correlation is also illustrated by Table II which shows mean values for the full term and premature deliveries

The differences are statistically highly significant, and the mathematical error is given



W ght of the pla enta — — — Maternal heart volume

Fig 1 A correlation between the infant s birth weight placental weight and maternal heart volume is shown

Table II

	Full Term	Prematures
Mean weight of placenta	6-7 ± 5 g	4"0 ± 8 g
Mean heart volume of the mother	669 ± 5 ccm	584 ± 8 ccm

B To find out how the physical constitution of the mother affects the size of the infant the mean weight and height of the mothers was calculated for both full term and premature deliveries The following results were obtained

Table III

	Full Term	Prematures
Mean weight of the mother	65 2 ± 0.4 kg	61 - ± 0 7 kg
Mean height of the mother	161 0 ± 0 3 cm	160 1 ± 0 4 cm

The table shows the means and the mathematical error The difference between the maternal weight of the full term group, 65 2 kg and that of the premature deliveries 61 2 kg was statistically highly significant there was no statistical difference between the respective maternal height values

C In the statistical analysis of the series the correlations be tween the infant s birth weight and the weight of the placenta, the mother s heart volume weight and height were calculated using

the analysis of variance method The results, the coefficient of correlation, the mathematical error and the degree of significance are given in Table IV

As will be seen from Table IV, there was a highly significant correlation between birth weight and placental weight in all the groups The correlation between the infant s birth weight and the mother's heart volume was highly significant for the series as a whole and for the deliveries at term On the other hand, within the premature group was no such correlation Between infant s birth weight and maternal weight the correlation was highly significant in the total series and the full term deliveries, but there was no correlation in the premature group The correlation between birth weight and the mother s height was significant in the total series and highly significant in the full term deliveries, but there was no correlation in the premature group

D The heart volume was correlated with maternal weight and height to establish whether the mother's heart volume was dependent on her physical constitution The correlation between maternal heart volume and placental weight was also calculated The results, the coefficient of correlation, the mathematical mean and the degree of significance are given in Table V

There was a highly significant correlation between the mother s heart volume and the weight of the placenta in the series as a whole and in the group of full term deliveries, and an almost significant correlation in the premature group The maternal heart volume showed a highly significant correlation with both maternal weight and height in all the groups

E Eleven per cent of the mothers had albuminuria and elevated blood pressure (over 135/80 mm Hg) at the end of pregnancy Fourteen per cent of the mothers in the premature group and 10 per cent in the full term group had these toxæmic signs If the material is divided into groups according to the mother s heart volume in cc and the weight of the placenta in g, the following incidence of toxæmia in the different groups is obtained

Tables VI and VII show that the incidence of toxæmia was higher when the mother s heart volume and placental weight were small

Table IV

	Full Term		Premature		Total Series	
Birth weight/Weight of placenta	0 56 ± 0 03	Highly significant	0 41 ± 0 07	Highly significant	0 69 ± 0 02	Highly significant
Birth weight/Heart volume of the mother	0 32 ± 0 04	Highly significant	0 09 ± 0 08	Not significant	0 38 ± 0 03	Highly significant
Birth weight/Weight of the mother	0 34 ± 0 04	Highly significant	0 10 ± 0 09	Not significant	0 32 ± 0 04	Highly significant
Birth weight/Height of the mother	0 [illegible] ± 0 04	Highly significant	0 11 ± 0 08	Not significant	0 15 ± 0 04	Significant

Table V

	Full Term		Premature		Total Series	
Heart volume of the mother/Weight of placenta	0 [illegible]1 ± 0 04	Highly significant	0 15 ± 0 07	Almost significant	0 3[illegible] ± 0 03	Highly significant
Heart volume of the mother/Weight of the mother	0 47 ± 0 04	Highly significant	0 54 ± 0 05	Highly significant	0 50 ± 0 03	Highly significant
Heart volume of the mother/Height of the mother	0 25 ± 0 04	Highly significant	0 33 ± 0 07	Highly significant	0 26 ± 0 04	Highly significant

Table VI

	Heart Volume of the Mother cc					
	– 400	401 – 500	501 – 600	601 – 700	701 – 800	801 –
Incidence of Toxæmia	22 %	8 %	11 %	11 %	8 %	13 %

Table VII

	Weight of the Placenta (g)				
	– 400	401 – 500	501 – 600	601 – 700	701 –
Incidence of Toxæmia	33 %	13 %	10 %	10 %	10 %

Discussion

It is known from earlier investigations that there is a correlation between the maternal heart volume and the infants birth weight If mothers with a small heart are given an opportunity to rest and thus ease the strain on their circulation the incidence of infants with a birth weight of under 2,000 g is reduced from 2 2 to 1 5 per cent and the perinatal mortality from 2 6 to 1 9 per cent (Räihä, Räiha *et al* 1959, 1956, 1957, 1963, and Unnerus, 1959) Interesting and valuable investigations on heart volume and -function have been made by Reindell *et al*, 1961, and Musshoff *et al*, 1961 Their results are essentially the same as ours

The following data on the circulation of blood in the uterus, placenta and kidneys are known from physiological and pathophysiological studies

The uterine circulatory minute-volume is about 750 ml at the end of the pregnancy and about 600 ml/min of this blood flows via the placenta The chorio decidual space of the placenta contains about 250 ml of blood The circulation of the placenta is about 1/10 of the cardiac output in rest and equal to that of the kidneys The placental circulation can fall to about 300 ml/min before fœtal anoxia ensues A fœtus weighing 3,000 g needs 25 ml of O_2 per minute, and this is obtained from 350 ml of blood when

the diffusion difference is 7 vol% The fœtal cardiac output is 450–500 ml/min and about 55 per cent of it flows via the placenta giving a blood circulation of 250–300 ml/min in the fœtal part of the placenta The maternal circulation to the placenta is influenced by a number of factors It is impaired by hypertension with toxæmic manifestations, muscular work and uterine contraction Even normal cases display degenerative changes in the placenta towards the end of the pregnancy, and they are accentuated if the placental circulation is obstructed and reduced (McClure Brown, 1954 1958 Dawes, 1958, Morris et al 1956, Metcalfe et al 1955 Weis et al, 1958, Sauramo, 1951, and Løvset et al 1957)

Owing to its ability to regulate the placental circulation by means of the paravillous circulation in the placenta, the fœtus has reserves which permit the maternal placental circulation to drop to nearly 1/3 of normal before fœtal anoxia ensues (Bøe, 1954) It has been noted furthermore, that the placenta synthesises progesterone which spreads to the uterine muscle reducing susceptibility to stimuli liable to produce contractions When the placental circulation is disturbed this mechanism is also upset and a premature delivery may ensue (Haskins et al 1954 Mastborn 1957 Pearlman 1954 and Zandler 1954)

The present investigation of the weight of the placenta and its relation to the infant s birth weight was planned with the knowledge of these facts in mind The weight of the placenta can be regarded as an approximate measure of placental circulation which means that the choriodecidual space c 250 ml as mentioned above and placental size must bear a certain ratio to the circulation This point is further supported by a study conducted by Secher et al (1962) which shows that the volume of blood which can be transported mechanically from the placenta to the fœtus immediately after parturition is correlated with the placental weight and fœtal birth weight Fig 1 and Tables I and II show clearly that the infant s birth weight is correlated with both maternal heart volume and placental weight Furthermore when the heart volume increases the placenta gains weight rapidly if the placental circulation remains good If the mother s heart volume is small and her organism strained the placental circulation suffers

Table VI

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shows clearly that there is a correlation between maternal heart volume and placental weight, and this provides further proof of the significance of the circulation for fœtal development The great importance of nutrition in pregnancy is obvious from the works of Thomson *et al* (1960, 1961) and Miller *et al* (1960)

Two authors, Hedberg and Radberg (1962), recently analysed a series of 80 normal deliveries and 80 deliveries leading to prematurity and drew the conclusion that neither the mother's heart volume nor her weight can be used to predict the infant's birth weight This study was reviewed in an article published in the USA (1962) It appears from the commentary that the editor unfortunately drew incorrect conclusions He refuted both the serviceableness of rœntgenologically determined heart volume as an index of the pregnant woman's blood volume and capacity for work and the importance of counselling, based on this measurement as prophylaxis for prematurity In addition, he questioned earlier results proving the value of these methods However an investigation by Raihä and Kauppinen (1963) comprising a series of about 20 000 patients makes it quite clear that the counselling work based on rœntgenological heart volume measurements results in a reduction by one third of the rate of small prematures and the perinatal mortality in premature infants

In 11 per cent of the present series there occurred towards the end of pregnancy symptoms of toxæmia in the form of albuminuria and elevated blood pressure This fairly high percentage is due to the high rate of prematurity in this series It is however interesting that toxæmia occurs in 14 per cent of deliveries before term and in 10 per cent of deliveries at term It appears from Tables VI and VII that the majority of toxæmic patients is to be found in the groups in which the mother has a small heart volume and a small placenta in other words when the mother's circulatory capacity is poor It is an acknowledged fact in the event of circulatory strain that the circulation of both the kidneys and the uterus becomes insufficient and the toxæmic effect on renal function during pregnancy is established in the works by Alvarez *et al* (1958) and Gylling (1961)

and the placenta develops less in size Räihä and Räihä *et al* (1959, 1956, 1957, 1963), Unnerus (1959) and Lesinski (1960) have previously emphasised that the infant's birth weight is dependent on the mother's heart volume, which is taken to be a standard of her blood volume

It appears from Table III that there is a significant difference between the body weights of mothers of full term infants and of premature infants, but no difference as regards maternal heights The latter observation conflicts with earlier reports by Thompson (1957), Billewicz and Thomson (1957), and Lesinski (1960) who established a correlation between maternal height and fœtal weight On the other hand, Lysgaard (1962) has shown *that there is a definite correlation between the gain in weight of* the mother during pregnancy and the birth weight of the newborn, and according to Thomson and Hytten (1960, 1961) the mother's weight gain during her first pregnancy is about 12 kg, and consists of the following components (a) fœtus, placenta and amniotic fluid 5 kg, (b) uterus and breasts 1 kg, (c) increased blood volume 1 5 kg, (d) increased extracellular fluid 1 kg and (e) storing of reserve nutrition 3 5 kg This distribution of the weight gain in pregnancy, with many factors loading the circulation, is clear evidence of the role of capacity for work of the pregnant mother s heart for the fœtal development On the other hand, the direct connection between the maternal heart volume and the mother s weight and height is clearly shown in Table V

Table IV shows the correlation of the infant s birth weight with the weight of the placenta, the mother s heart volume, weight and height Taking the series as a whole the infants birth weight was *influenced by all these factors, but in particular by placenta* weight and maternal heart volume The same relationship prevailed in the group of full term deliveries, but the premature groups was different The birth weight of the premature group was correlated with the size of the placenta but not with the mother s heart volume, weight or height The main conclusion to be drawn from this is that the mother s physical constitution was not a significant factor in prematurity in the present series, in which the gestational age is unrecorded On the other hand, placental size and, consequently, placental circulation were important factors Table V

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Received on Feb 23rd 1963

Conclusions

The following conclusions can be drawn from the study

1 The infant s birth weight is influenced by the mother's capacity of work which can be measured as her heart volume

2 The weight of the placenta is a good standard of placental circulation, and the placental weight is correlated with the infant's birth weight The placental weight is also correlated with the mother s heart volume

3 The infant's birth weight is correlated with the mother s weight and not, in Finland, with her height As the mother s weight and above all weight gain during pregnancy is governed by the blood circulation the obvious correlation between the mother's weight and the infant s birth weight is *de facto* a correlation between the mother s circulatory capacity and the infant s birth weight

4 The fact that the majority of the cases of toxæmia are encountered in mothers with small heart volumes and small placentæ shows the significance of circulation for both fœtal development and renal function during pregnancy

SUMMARY

The correlation between maternal heart volume, maternal height and weight, and placental weight and the infant s birth weight was studied in a series of 704 deliveries The results are given in the section 'Conclusions

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The statistical analysis was performed by M Karhunen Ph D

Material and Methods

The blood samples were acquired from maternity hospitals and antenatal clinics In no instance was anticoagulent present The blood was taken in vacutainers (Venülen),[1] the clot was not allowed to retract for more than 24 hours and the serum collected after centrifugation was stored at −70° C in a deep-freezerefrigator

The control group studied at the same time, comprised healthy non pregnant women of the same ages The growth behaviour of cells was recorded after 24 hours of culture the clumping test" was performed as follows (For more details see Saxen and Penttinen 1961)

The clumping test

1 Stock culture HeLa cells maintained in Roux bottles containing 70 ml of growth medium consisting of 30 per cent heat inactivated (56° C) filtrated unselected human serum pool in Hanks solution Growth time 2–3 days

2 Trypsinization 30 min at 36° C Calculated final concentration of 0 15 per cent of the trypsin preparation in Hanks solution

3 Inoculum 20 000 cells in test tubes of 16 × 120 mm

4 Culture medium One ml fresh human serum 90 30 or 10 per cent in Hanks solution and 0 05 ml of tris buffer (pH 7 2)

5 Recording The growth behaviour was recorded after 24 hours stationary incubation using an ordinary microscope

6 Controls a) "old" non heat inactivated serum pool b) known fresh clumping serum c) known fresh non clumping serum

In each case the growth behaviour of cells was recorded without knowledge of the set up of the experiment The sera were divided into four groups

[1] Behringwerke A G Marburg Lahn

Meyer B Penttinen K and Saxen E. Acta obst. et gynec scandinav 4 —, 1963

From the Departments of Virology (Professor N Oker Blom) and Pathology (Professor E Saxén), University of Helsinki, and from the Second Clinic of Obstetrics and Gynæcology (Professor P Vara), Helsinki University Central Hospital, Finland

THE EFFECT OF PREGNANCY ON THE CAPACITY OF SERUM TO CONTROL AND PROMOTE GROWTH IN CELL CULTURE

BY

B MEYER K PENTTINEN AND E SAXÉN

There exist great differences in the capacity of fresh individual human sera to control and promote growth of cells in cell culture (Saksela, 1962 Penttinen and Saxen, 1959, Saxen and Penttinen, 1962) This has been observed by examination of the growth behaviour of cells, be measuring the nuclear counts by cell nitrogen determination, and by chromosomal studies These methods have made it possible to divide sera into two extreme and one or two intermediate groups In one extreme group, the cells are in dense clumps and the growth rate is low, in the other the cell growth is very good and occurs in monolayers

The incidence of these two extremes varies in different groups classified by age and disease of the donor and preliminary studies have indicated that normally the growth in serum from pregnant women is good (Penttinen and Saxen, 1962)

There thus appeared to be justification for more detailed study of this effect by observation of the growth behaviour of cells in serum taken at different phases of pregnancy This could also throw some additional light on the mechanism of the clumping phenomenon, and on the factors which influence cell contact and adhesion

Table II *Frequency of Clumping of Cells in Early and Late Pregnancy and in Non Pregnant Women of the Same Age*

Source of Serum	Total No of Cases	Growth Behaviour of Cells, Degree of Clumping			
		No Clumping		Clumpin	
		1	2	3	4
Pregnant women (5 28 weeks)	45	25	19	1	0
Pregnant women (29–40 weeks)	45	16	20	5	4
Non pregnant women	34	2	10	19	3

weeks of pregnancy In the 45 sera from the latter part (29–40 weks) of pregnancy nine displayed some kind of growth controlling effect against 21 of the 34 control sera The growth was notably good in about half of the pregnant sera but in less than 10 per cent of the control sera

The good growth promoting effect of fœtal serum obtained from the umbilical cord was also noted, and the relatively *high* frequency of clumping sera among samples taken during delivery and six days post partum is also of interest.

The clinical data were carefully investigated and attention was paid to the following age pathological obstetrical data birth weight and sex of the child and also to the medication given However no correlation was observed between these and the growth promoting capacity of the respective sera

SUMMARY AND DISCUSSION

The main observation was that the serum lacked growth controlling effect during the 5–20 weeks of pregnancy Also noteworthy was the *high* proportion of clumping sera six days *post partum* together with their frequent occurrence in complicated pregnancies (toxæmias prolonged pregnancies placenta praevia abruptio placentæ and diabetes) The group of strong clumping

1 *Excellent growth,* as in 'old non-heat inactivated serum pool No clumping of cells even in 90 per cent serum

2 *Good growth* No clumping in 30 per cent serum, but some clumping in 90 per cent serum

3 *Intermediate growth* Occasional clumping in 30 per cent serum

4 *Poor growth* Distinct or strong clumping in 30 per cent serum Very few or no cells seen between the clumps, poor or no growth in 90 per cent serum

Results

The results are shown in Tables I and II

Table I *Frequency of Clumping and Non Clumping Serum in Different Phases of Pregnancy, Puerperium, and Lactation*

Growth Behaviour of Cells Degree of Clumping		Duration of Pregnancy in Weeks 5–12	13–20	21–28	29–32	33–36	37–40	Partus	6 Days Post Partum	6 Weeks Post Partum	Complicated Pregnancy	Cord Serum	Non Pregnant Women
Total		16	14	15	8	19	18	19	18	16	26	6	34
No clumping	1	9	6	10	1	8	7	12	5	9	8	6	2
	2	7	8	4	5	6	9	3	6	7	10	0	10
Clumping	3	0	0	1	1	4	0	2	1	2	3	0	19
	4	0	0	0	1	1	2	2	6	0	5	0	3

1 No clumping Excellent growth
2 No clumping Good growth
3 Some clumping Intermediate growth
4 Strong clumping Poor growth

No growth-controlling effect (no cell-clumping) was observable in the serum samples from the 5–20 weeks of pregnancy The first strong clumping effect was found in sera of the 29–32

Fylling Petter Acta obst. et gynec scandinav 42 227 1963

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SERUM AND PLASMA OXYTOCINASE ACTIVITY DURING INDUCTION OF LABOUR

BY

PETTER FYLLING

The ability of pregnant sera or plasma to inactivate oxytocin was first observed by Fekete (1930) The inactivating capacity increases as pregnancy advances Following the establishment that the inactivation is enzymatic in nature (Werle *et al* 1941), the reaction has been studied by several investigators by means of a biological method (Page 1946, Werle and Semm, 1946)

The elucidation of the structure of oxytocin independently by du Vigneaud *et al* and Tuppy in 1953, resulted in more detailed investigations of the mechanism of inactivation of the hormone by the enzyme oxytocinase which is present in pregnant serum or plasma

In 1957 Tuppy and Nesvada localized the site of action of the enzyme to the peptide bond between the tyrosine and cystine residues of the oxytocin molecule They also described a method for estimating the enzyme using the synthetic L-cystine-di β-naphthylamide

According to Dicker and Tyler (1956) as well as Hilton and Johnson (1959) the capacity of pregnant serum to inactivate oxytocin decreases from the 28th week and at term little or no activity could be detected.

The reduction in serum oxytocinase activity near term may provide an attractive explanation for the increase in uterine sen-

sera comprised 17 cases Among these, only four out of a total of 90 sera were from normal pregnancies, six were *post partum* sera, five belonged to the complicated pregnancy group, and two were taken during delivery

Since the frequency of clumping and non clumping sera in pregnancy *is so different from that observed in non pregnant* women of the same age, it is obvious that pregnancy has an effect on the growth-controlling capacity of the serum The changes in the serum which occur during pregnancy and are responsible for the differences in the growth behaviour of cells in cell culture are unknown The more frequent clumping of cells at the end of pregnancy could be connected with the increase in *e g* β *lipoproteins at that time* (de Alvarez, 1959, Saxen, 1961) The obvious disappearance of the clumping phenomenon after the first weeks of pregnancy remains unsolved

In this connection, one fact to be borne in mind is that clinical experience has shown that mammary cancer grows more quickly in early pregnancy than in the later stages (Schmid, 1961), furthermore the rapid growth of other tumours during pregnancy, the occurrence of *lesions resembling carcinoma in situ* of the cervix, and "granuloma gravidarum have also been reported

POST-SCRIPT

After submitting this paper for publication a most interesting investigation came to the authors attention Investigations of the influence of sera from pregnant women on the growth of cell cultures in conjunction with the occurrence of abnormal α lipoprotein (*J Rejnek T Bednarik E Rerdbkova* and *A Dolezal* Clin Chim Acta *6* pp 108—115 1963)

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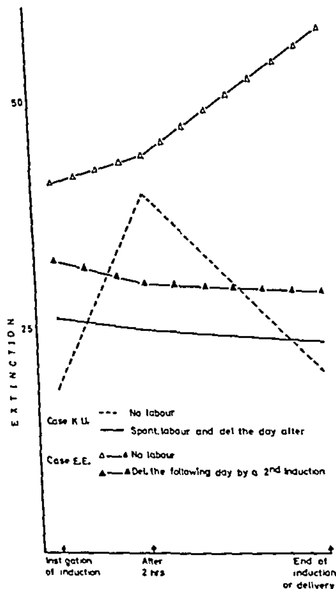


Fig. 2 This figure represents the two cases K.U. and E.E. listed in Table I and demonstrates the oxytocinase activity in plasma exposed to siliconized glass and plastic

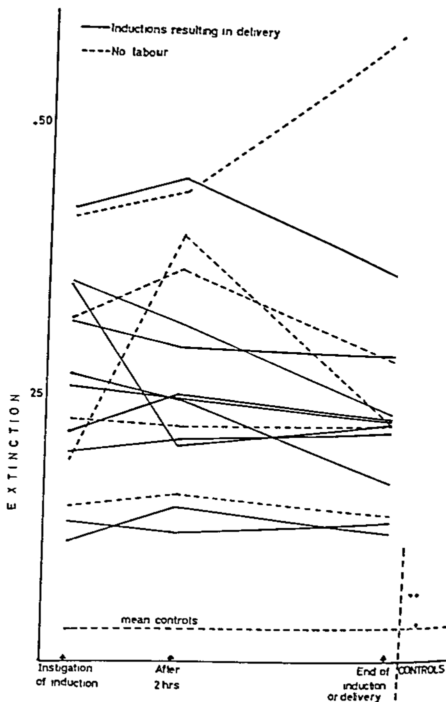


Fig 1 This figure represents the 13 first cases listed in Table I, and demonstrates the oxytocinase activity in plasma exposed to siliconized glass and plastic

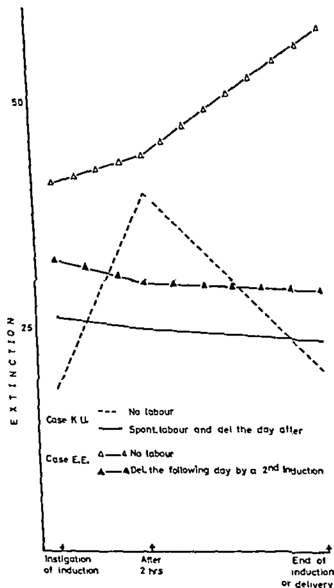


Fig 2 This figure represents the two cases K U and E E listed in Table I and demonstrates the oxytocinase activity in plasma exposed to siliconized glass and plastic

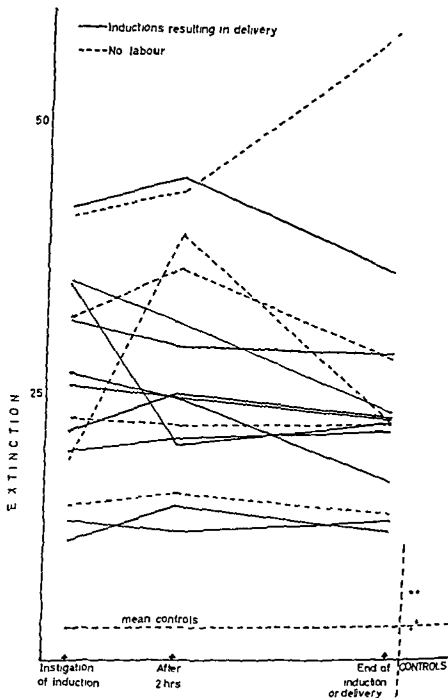


Fig 1 This figure represents the 13 first cases listed in Table I, and demonstrates the oxytocinase activity in plasma exposed to siliconized glass and plastic

pregnancy (i e past estimated term), Rh isoimmunization, toxæmia, uterine inertia, placental insufficiency and intrauterine foetal death

Twelve healthy, non pregnant women, 18–25 years of age, served as controls

Eight of the inductions were unsuccessful in that no labour or even moderate uterine contractions ensued. One patient did not start in labour during the induction, although spontaneous labour occurred and delivery followed within a few hours on the following day (Fig 2) The plasma samples, in this case, were obtained in the usual manner during induction, and also on the next day at the beginning of spontaneous labour, as well as at delivery In a second case (Fig 2) labour failed to start on the first day by means of Pitocin given by intravenous drip, but the day after this delivery occurred. Plasma samples were obtained on both days by the method to be described

The first blood sample was obtained at the *instigation* of the induction The second sample was taken 2 hours later, and the third at the time of delivery or at the end of an unsuccessful induction

Collection of the samples

1 *Serum* About 5 ml blood was delivered from the antecubital vein through Wasserman needles into unsiliconized glass test tubes, allowed to coagulate at room temperature and then centrifuged at 3000 r p m for 5 minutes The serum was pipetted off into another unsiliconized glass test tube

2 *Plasma* 4 5 ml blood was withdrawn through siliconized Wasserman needles into a) Lusteroid test tubes, b) unsiliconized glass test tubes to which had been added 0 5 ml of 3 1 per cent Na citrate The samples were centrifuged within 15 minutes at 3000 r p m for 5 minutes and the plasma from tube a was pipetted (siliconized pipette) into another Lusteroid test tube, while plasma from tube b was delivered into an unsiliconized glass test tube All samples were deepfrozen within one hour and stored for up to 4 weeks before analysis Standing for one hour at room temperature does not affect the activity of the enzyme

sitivity to oxytocin The changes in oxytocinase activity might be considered a physiologically protective measure in keeping the uterus at rest during pregnancy It has been demonstrated that when oxytocin is infused, the oxytocinase activity of the plasma increases (Caldeyro-Barcia and Poseiro, 1958) Such a protective mechanism during pregnancy would be complimentary to the reduction of uterine irritability by sex-hormone action

From present evidence, however, it is unlikely that the decrease in oxytocinase activity occurs shortly before the onset of labour (Werle and Effkemann, 1941, Page, 1946, Werle and Semm, 1956, Caldeyro-Barcia and Poseiro, 1958, Hartburg-Muller, 1960, Titus *et al*, 1960, Centario *et al*, 1961, Semm, 1961) Thus in contrast to Dicker and Whyley (1959), Timoshenko (1961) observed higher enzyme activity in parturient women with uterine inertia than in those with normal uterine contractility

The site of production of oxytocinase is generally believed to be in the placenta (Page, 1946, Hawker, 1956, Tuppy and Nesvada, 1957, Page *et al*, 1961) Additional evidence on the site of origin of the enzyme is constituted by the findings of Semm (1961) to the effect that high enzyme activity was found in the vesicular fluid of vesicular moles and in the syncytiotrophoblast

Theoretically, the equilibrium between hormone release and oxytocinase action could be disturbed either because too little oxytocin is produced or because the concentration of oxytocinase is abnormally altered The presence of oxytocinase in the circulation may also explain why injection of oxytocin fails to induce labour Accordingly, the work here presented deals with

a) The oxytocinase activity in serum and plasma during induction of labour, whether delivery resulted or not
b) The effect of siliconized glassware and plastic material on the plasma oxytocinase activity

Material and Methods

The investigations were made on 21 pregnant women, 18–44 years old The indications for induction of labour were prolonged

Oxytocinase Activity in Serum or Plasma						
1st Sample		2nd Sample		3rd Sample		
S+	S−	S+	S−	S+	S−	Comments
198 ± 021	358 ± 016	208 ± 016	320 ± 010	220 ± 030	285 ± 000	Pitocin i m 2 days prior without effect
352	255	314	347	234	310	Pitocin drip 2 days prior without effect
215 ± 013	203 ± 009	250 ± 003	216 ± 029	224 ± 008		Parabuccal tabl 3 days prior without effect
422 ± 038	635 ± 000	450 ± 015	536 ± 011	365 ± 010	512 ± 012	Pitocin i m 7 and 4 days prior without effect
129 ± 004	205 ± 000	120 ± 000	192 ± 012	132 ± 002	183 ± 003	
267 ± 008	213 ± 013	248 ± 004	181 ± 041	164	258 ± 002	
350 ± 000	445 ± 045	201	445 ± 003	227 ± 002	228 ± 003	
113	172	143	160	130	180	
181	354	398	278	222	346	
257	326			225	272	Spontaneous labour the following day
412	467	438	760	580	700	
319	550	295	447	287	523	A and induction on the following day
320 ± 038	320 ± 010	365 ± 005	257 ± 003	282 ± 027	262 ± 013	Pitocin i m 5 and 3 days prior without effect
227 ± 002	289 ± 017			218 ± 003	325 ± 002	

Table I

	Age	Para	Pregnancy State in Weeks	Indications	Methods	Effect
*	26	1	38	Toxæmia	Pitocin i v drip	Del a. 8 hrs
*	24	3	40	Toxæmia	Pitocin i v drip	Del a 3 hrs
*	28	3	38	Rh isoimmunization	Pitocin i v drip	Del a 2 hrs
	44	12	36	Intrauterine fœtal death	Pitocin i v drip	Del a. 9 hrs
	29	2	40	Uterine inertia	Pitocin i m	Del a 8 hrs
*	31	2	42?	2 weeks past estimated term	Pitocin i m	Del a 21 hrs
	34	1	40	Uterine inertia	Pitocin i v drip	Del a. 6 hrs
	29	3	40	Rh isoimmunization	Pitocin i v drip	Del a 3 hrs
*	27	3	40	Uterine inertia	Pitocin i m	No labour
	27	3	40	Spontaneous labour		Spontaneous labour and delivery
	40	3	36	Toxæmia	Pitocin i v drip	No labour
	40	3	36	Toxæmia	Pitocin i v drip	Del a. 20 hrs
*	30	3	38	Placental insufficiency	Pitocin i v drip	No labour
	18	1	40	Rh isoimmunization	Pitocin i m	No labour

Oxytocinase Activity in Serum or Plasma						
1st Sample		2nd Sample		3rd Sample		
S+	S−	S+	S−	S+	S−	Comments
146 ± 004	200 ± 000	155	200 ± .000	137	177 ± 002	
	346		366		396	Pitocin i.m 9 6 and 4 days prior without effect
	330		265		252	Pitocin i.m 15 and 6 days prior without effect
	356				325	
	340		330		318	A 2nd induction on the following day
	225		345		340	
	375 ± 005				350 ± 050	Pitocin i v 3 days prior without effect
	421 ± 004		.445 ± 000		501 ± 003	
	280		270		310	Pitocin i.v 7 days prior without effect
	440		455		395	

Oxytocinase activity is expressed as extinction readings in spectrophotometer at 365 μ

Results and discussion

As appears from Table I and Fig 1 the oxytocinase activity in serum or plasma varied considerably in contrast to the controls However the mean activity for the controls was significantly lower than in the experimental cases

In plasma exposed to siliconized glass and plastic there were except in three cases but small variations in the enzyme activity during induction of labour, and it made no significant difference whether delivery ensued or not (Fig 1) Furthermore the results

...se	Age	Para	Pregnancy State in Weeks	Indications	Methods	Effect
.A *	30	1	42?	2 weeks past estimated term	Pitocin i m.	No labour
S †	33	3	40	Rh isoimmunization	Pitocin i v drip	Del. a. 9 hrs
N †	24	2	40	Uterine inertia	Pitocin i v drip	Del. a. 4 hrs
S †	39	4	38	Rh isoimmunization	Pitocin i.v drip	No labour
S †	39	4	38	Rh isoimmunization	Pitocin i v drip	Del a. 4 hrs
G †	37	5	42?	2 weeks past estimated term	Parabuccal tablets	Del a. 7 hrs
H †	25	2	40	Rh-isoimmunization	Pitocin i v drip	Del. a. 9 hrs
..†	32	4	38	Rh isoimmunization	Pitocin i v drip	Del a. 4 hrs
†	34	2	40	Toxæmia	Pitocin i v drip	No labour
H †	32	3	40	Uterine inertia	Pitocin i m	No labour

Siliconized glassware and plastic material
Unsiliconized glassware
Plasma
Serum
| a Delivery after

All of the samples from individual patients were tested simultaneously in order to avoid methodological errors

Usually, duplicate measurements of enzymatic activity were carried out, according to the method of Klimek & Pietrzycka (1961) The colour densities were measured in a spectrophotometer at 565 μ

The values given in Table I represent the extinction readings

that from the uterus some of the preformed enzyme enters the circulation, *i e* it may be a matter of release and not a matter of increased formation There is some disagreement between the present results and those of Mendez Bauer and Tuppy (1959) to the extent that increased oxytocinase activity follows oxytocin infusion Further studies in this direction are being undertaken

Clinical experience suggests that in atonic uterine bleeding, injections of oxytocin intravenously are sometimes ineffective, whereas intrauterine (intramural) injections usually are effective Semm (1959) stated that oxytocin injected into the myometrium acts locally and is more effective because it is protected from plasma or serum oxytocinase In other words, the equilibrium between oxytocin release and oxytocin inactivation may in one way or another be upset Another explanation may be that it is a matter of oxytocin concentration In contrast to oxytocin injected into the myometrium, the intravenously injected oxytocin becomes diluted in the circulating blood so that it reaches the uterus in low concentration

The present work includes too few cases to permit decisive conclusions as to the effect of oxytocinase in keeping the pregnant uterus at rest However, the results indicate that other and probably more important factors are involved in the process

SUMMARY

1 The serum and plasma cystine aminopeptidase (oxytocinase) was determined during induction of labour The reasons for induction of labour were prolonged pregnancy Rh isoimmunization toxæmia uterine inertia placental insufficiency and intra uterine fœtal death

2 The values obtained showed a high degree of variation, without any obvious correlation to the different pregnancy disorders The measurements also revealed great variations in the same individual during induction of labour without any typical rise or fall during the period of investigation

3 In plasma exposed to unsiliconized glassware the values tended to be higher than in plasma placed in siliconized glassware

did not indicate any relationship between enzyme activity and the pregnancy disorders

In 33 out of 42 measurements, plasma activity was higher for the samples exposed to unsiliconized glass There were considerable variations in the values of the two groups (range 0.01–3.22) as well as in individual cases (Table I) However, the variations were unrelated to any of the pregnancy disorders

The serum measurements also exhibited great group and individual variations, but the values were of approximately the same level as in plasma exposed to unsiliconized glassware

There is good agreement between the present data and those from other reports as to the increase in serum or plasma activity during pregnancy However, the present results did not confirm the observation of Caldeyro-Barcia and Poseiro (1958) to the extent that when oxytocin is infused, increased oxytocinase activity of the plasma occurs

Except for one case a significant fall in plasma or serum enzyme activity prior to labour could not be demonstrated

The hydrolysis of cystine-di-β naphthylamide by cystine aminopeptidase in nonpregnant serum or plasma is of a measureable order, whereas oxytocinase activity as measured by the biological method is negligible (Page *et al*, 1947) The synthetic naphthylamide substrate is to a slight extent split by nonpregnancy serum or plasma, but this activity can be separated from the specific pregnancy enzyme by electrophoresis

Labour and delivery are in some respects comparable to physical exercise and some surgical interventions These latter have been found to cause an elevated activity of plasma oxytocinase (Klimek *et al*, 1962), hence increased oxytocinase activity during labour and delivery would not be entirely unexpected. However, the present investigations revealed that if there were any differences, the activity rather tended to decrease during labour

Mendez-Bauer and Tuppy (1959) have, independently, observed some increase in oxytocinase activity after parturition and after induction of labour by Syntocinon (Syntocinon, Sandoz) However, their observations need not mean that formation of oxytocinase *was stimulated* A *possible* explanation could be

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or plastic material The serum values were of approximately the same level as in plasma exposed to unsiliconized glassware

4 The results indicate that there must be other and probably more important factors than oxytocinase keeping the uterus at rest or initiating labour

Acknowledgement

I am grateful to Ph D and Odont D S D Schultz Haudt for his many valuable suggestions in the preparation of this manuscript I also would like to express my gratitude to Professor E. Schjott-Rivers and Professor O Torgersen for their cooperation which was essential to this investigation

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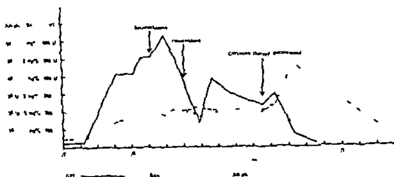


Fig 1 Diagram showing the laboratory findings of alkaline phosphatase (Alk ph) serum bilirubin (Bil/s) and glutamine puruvic acid transaminase (GPT)

restless but drowsy Increasing severity in the degree of hepatosis indicated the necessity for termination of the pregnancy On January 14th artificial rupture of the membranes was performed Five days later the serum bilirubin was 6 3 mgm % G P T 15 units Subsequently liver function rapidly returned to normal

In 1962 she became pregnant for the second time The last regular menstrual period began on January 14th 1962 In the 27th week of gestation lassitude and itching appeared followed by jaundice On July 24th 1962 when 27 weeks pregnant she was again admitted to the Obstetrical and Gynæcological Department Central Hospital Ängelholm On admission jaundice was manifest She had many scratch marks on her trunk and extremities Her blood pressure was 150/100 mm/Hg Laboratory findings Bil/s 2 mg per cent alk ph 14 U thymol turbidity 0 05 GPT 415 U By August 8th the itching and jaundice had increased she became restless but drowsy Epigastric pain developed and the liver was tender and enlarged The serum bilirubin was 4 7 mgm % and the G P T 500 units Because of the severity of the hepatosis termination of pregnancy was again considered However as she had no living child she was very anxious that the pregnancy should continue Any further pregnancy would probably follow the same course as the previous and current pregnancies It was considered that isoimmunisation might be an ætiological factor in this case and therefore cortisone therapy was commenced

From 8th–13th August she was given 4 mgm betamethasone daily The dose was then reduced to 2 mgm daily On August 21st the serum bilirubin was 2 mgm % and the G P T 390 units On August 23rd triamcinolone therapy was commenced in an attempt to improve the results obtained using *betamethasone 16 mgm daily* triamcinolone was given and by August 28th the serum bilirubin was 1 8 mgm % and G P T 140 units On August 31st the dose was reduced to 12 mgm daily and this was maintained until delivery on September 29th After reduction of the triamcinolone dose the G P T

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CORTISONE THERAPY OF JAUNDICE IN PREGNANCY

BY

JAN MOLANDER AND FINN WICKSELL

Jaundice of non-infectious origin beginning during pregnancy, so-called hepatosis, as a rule has a benign course In some cases signs of serious liver damage may appear The condition can then rapidly develop into so-called obstetric yellow atrophy This carries a poor prognosis and may endanger the patient s life Until now, it has been thought that interruption of the pregnancy was necessary to stop the progression of the condition, the cause of which is not clearly understood Recently it has been suggested that iso-immunisation might be the cause of the hepatosis, Sheehan (1961), Boquien *et al* (1961) If this were so, cortisone therapy would be expected to have a favourable effect Since no such trials as yet have been published the following case is of interest

The patient is a 30 year old woman In 1955 cholecystectomy and appendicectomy were performed In 1959 during her first pregnancy, jaundice appeared in the 19th week On December 16th 1959 she was admitted to the Obstetrical and Gynæcological Department Central Hospital Ängelholm On admission jaundice was manifest and she had scratch marks on her trunk and extremities Laboratory findings on December 16th 1959 Hæmoglobin level (Hb) 80 %, red blood count (R) 3 8 million/cu mm, serum bilirubin (Bil/s) 6 3 mg per cent alkaline phosphatase (alk ph) 19 units (U) thymol turbidity 0 02, glutamine pyruvic acid transaminase (GPT) 448 units (U), diastase in the urine 64 Urinary sed no abnormality

During her stay in the hospital the skin irritation and jaundice increased In addition she developed pain in the epigastric region and the liver was found to be tender and enlarged In the 24th week of gestation she became

SUMMARY

The patient, a woman aged 30, developed serious hepatosis with impending transition into obstetric yellow atrophy during two consecutive pregnancies In 1959 the pregnancy had to be terminated because of the severity of the hepatosis During the second pregnancy in 1962 treatment with cortisone resulted in improvement sufficient for the pregnancy to continue, with the birth of a healthy child In the opinion of the authors this result was made possible by the cortisone therapy The possibility that the hepatosis was caused by isoimmunisation is discussed The good result of the therapy gives support to this hypothesis

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rose to 300 units and remained at this level until after delivery The serum bilirubin remained at 2 mgm % and alkaline phosphatase at 20 units During the period prior to delivery her condition improved The restlessness and drowsiness disappeared gradually and the jaundice decreased When therapy was begun it had been the intention to terminate the pregnancy when a viable fœtus could be expected Because of the patient s response to therapy spontaneous delivery was awaited

On September 30th a normal female infant weighing 2750 g was delivered without complication During her stay in the Pediatric Department from the 30th of September till the 5th of October she behaved normally and no signs of adrenal cortical insufficiency were seen. The twentyfour hour urinary total corticoids amounted to 0 8 mg

Discussion

In the described case severe hepatosis (obstetric yellow athropy) developed in two consecutive pregnancies In the first pregnancy jaundice became apparent in the 19th week and the patient s condition worsened so that termination of the pregnancy became imperative by the 24th week In the second pregnancy jaundice developed later, in the 27th week, and the course followed that of the previous pregnancy with increasing disturbance of liver function Since we considered that isoimmunisation was possible ætiological factor in the case cortisone therapy was started in the 31st week and continued until delivery was accomplished in the 37th week During the period of treatment, there was marked improvement both in the symptoms and in the laboratory findings (Fig 1)

Cortisone therapy in pregnancy for reasons other than jaundice has been described by several authors, Katzenstein *et al* (1954), Gelle *et al* (1956), Harries *et al* (1956), Hottinger (1959), Itelson *et al* (1961), Lohmeyer (1961) In some cases fœtal defects have been seen Gelle *et al* (1956), Harries *et al* (1956), but it has not been possible to show a certain relation between these and the treatment In our case no harmful effect on the child could be detected In our opinion the cortisone treatment made it possible to continue the pregnancy and achieve the birth of a healthy baby The result of the treatment gives strong support to the isoimmunisation theory

pears elsewhere (Jacobson 1963), this paper is restricted to the principal features of the analysis

The series comprises 543 consecutive primigravidæ, aged 35 or more at the time of delivery, the upper age limit being 47 years These deliveries took place in the department during the eleven year period 1950–60 and there were 550 infants (8 pairs of twins where one of the infants was stillborn with a birthweight of 410 g and therefore registered as an abortion) The elderly primigravidæ constituted 2 1 per cent of all women delivered at the department during the period in question (25 910 cases)

Throughout the entire analysis the series was subdivided into three arbitrary age groups namely 35–36 years (228 cases) 37–39 years (212 cases) and 40 years or more (103 cases) thus making it possible to study the influence of ageing Furthermore, the principles of the clinic as regards obstetrical management dif fered in some respects (see below) during this period between elderly primigravidæ above and below 40 years of age This ren dered possible comparisons of therapeutic measures between sub-groups within the series making a better basis for conclusions than do comparisons between quite separate series

Statistical differences were analysed for significance by the χ method a probability of 5 per cent or better being regarded as significant

As an expression in relative terms for the rapid *decline in fer tility* with increasing age it was found that of those women who were 35–36 years of age at the time of their first delivery 25 per cent subsequently gave birth to one child or more during the ob-servation period which varied from 1 to 12 years whereas the corresponding figure for those in the highest age group (over 40 years) was less than 9 per cent

Correlation of different *durations of marriage* (or cohabita tion) with various prognostic parameters such as complication rate during pregnancy operative delivery rate and perinatal mor tality led to no conclusions which could be construed to support the well known opinion of Meyer (1916) and subsequent ob-servers According to Meyer it is possible to discern two separate prognostic groups of elderly primigravidæ namely the consti tutionally weak who despite ample opportunity do not conceive until late and the constitutionally normal in whom late concep-

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THE ELDERLY PRIMIGRAVIDA

A study of 543 cases

BY

LENNART JACOBSON

Primigravidæ over the age of 35 years are known to form a prognostically unfavourable obstetric group, this being reflected particularly in the perinatal mortality figures (*cf* Schlesinger and Allaway, 1957, Kærn, 1960, Hesselsjö and Ånberg 1962) Varying principles for the obstetrical management of these patients, together with widely diverging results, have appeared in the literature (se review *e g* by Bergman, Malmström and Schöön, 1961) Dissimilarities in the composition of the reported series often render objective judgements and comparisons of the results difficult In a few recent Scandinavian investigations a distinctly improved infant prognosis as a result of modern obstetrical principles has been reported (Bergman, Malmström and Schöön, 1961, Kærn, 1962)

In an attempt to illuminate the present general situation with particular regard to the prognostic significance of various clinical factors in this category of patient, an eleven-year series of elderly primigravidæ, collected from the Department of Obstetrics and Gynæcology, Lund, was submitted to thorough analysis As a result of medical and administrative circumstances, both local and general for the country, the clinical material in this series fulfils strict requirements as regards homogeneity and can be regarded as a representative cross section of the population

As an extensive and detailed report on this investigation ap-

rates in the various age groups of elderly primigravidæ The incidence of complications was found to rise with increasing age Statistically significant differences were found throughout between the lowest and the highest age groups (P being < 0 02 as regards complications during pregnancy and < 0 01 as regards complications in labour and the puerperium) Concerning the labour complications a significant difference was also found between the middle and the highest age groups (P < 0 01)

The complications during pregnancy labour and the puerperium respectively were mutually correlated This can be readily deduced from Table III and shows the prognostic importance

Table III *Prognostic Comparison of Cases With and Without Pregnancy Complications*

	Uncomplicated Cases	Complicated Cases	Difference
Number of cases	195	348	
Median (P_{50}) of age yrs	37 1	37 6	
Spontaneous deliveries			
number	124	192	
per cent	63 6	55 2	P < 0 05
Vaginal delivery operations			
number	50	80	
per cent	25 6	23 0	insign
Cæsarean section			
number	21	76	
per cent	10 8	21 8	P < 0 01
Complications during labour and delivery			
number of cases	90	191	
per cent	46 1	54 9	P < 0 05
Puerperal complications			
number of cases	58	191	
per cent	29 7	54 9	P < 0 001
Infants			
Premature (< 2 500 g) per cent	5 6	9 9	insign
Postmature per cent	21 5	17 5	insign.
Perinatal mortality per cent	3 6	4 9	Insign.

According to the Clifford Score

tion is the result of extraneous circumstances. In the present series no statistically significant differences were found between those women who had been married for more and less than 5 years respectively.

Maternal morbidity. There was no maternal death. The percentage frequencies of complicated cases during pregnancy, labour and the puerperium are shown in *Table I*. Since all compli-

Table I. *Percentage Frequencies of Complicated Cases in the Series of Elderly Primigravidæ, and an Overall Obstetric Series of the Department*

	Elderly Primigravidae (543 Cases)	Total Series (4 685 Cases)	P
Pregnancy complication rate	64.1	30.2	<0.001
Delivery complication rate	51.7	8.0	<0.001
Puerperal complication rate	45.9	17.0	<0.001

cations, even those of minor clinical importance were recorded, the figures obtained are somewhat higher than in the majority of reported series. *Table I also gives a comparison with the morbidity* of another series, comprising all obstetric cases of this department over a two-year period, in all 4,685 cases, analysed in an identical way by Bengtsson (1959). When morbidity figures of the two series were compared, statistically significant differences were observed throughout ($P < 0.001$). This illustrates the highly increased morbidity among elderly primigravidæ as compared with the overall obstetric population.

In Table II a comparison is given between the complication

Table II. *Percentage Frequencies of Complicated Cases in Different Age Groups of Elderly Primigravidæ*

	35–36 Yrs (228 Cases)	37–39 Yrs (212 Cases)	≥40 Yrs (103 Cases)
Pregnancy complication rate	58.3	66.5	71.8
Delivery complication rate	44.3	51.4	68.9
Puerperal complication rate	39.0	48.6	55.3

the perinatal mortality the latter being in remarkable contrast to the results quoted in most other reported series This might be attributed to the extensive antenatal care and generous admission to hospital which according to the principles of the department was offered to these patients

Vaginal bleeding of undiagnosed nature during pregnancy was found to be a complication associated with a very unfavourable prognosis, particularly for the child Of 27 infants born to 26 such patients 5 succumbed in the perinatal period, a mortality rate of 18 5 per cent Placental abnormalities were common at delivery in 6 cases previously undiagnosed placenta prævia was detected, and in 2 cases premature separation of placenta occurred In fact, vaginal bleeding of this kind was one of the complications correlated with the highest perinatal mortality figures being surpassed only by breech presentation and prematurity

Labour Labour was characterised by an increased incidence of uterine inertia fœtal distress intra partum fever, and toxæmia The total incidence of complications during labour is given in *Tables I and II* The rate of premature rupture of the membranes (30 6 per cent) was considerably higher than in the total obstetric series of the department Furthermore the elderly primigravidæ suffered greater loss of blood and more frequent injuries of the vagina and perineum than other patients The distribution of the various fœtal presentations revealed no significant divergence from that in the total series

The increased incidence of complications during delivery and hence the close obstetrical supervision of these cases led to the more frequent use of X ray examinations of the fœtus and birth canal during or prior to the onset of labour Such examinations were carried out in 36 6 per cent

Cæsarean section was performed before the onset of labour in 55 patients the majority of these being aged 40 and over The median value for the duration of labour in the remaining cases lay within the limits usually set for any primigravida regardless of age In 133 cases (24 5 per cent) however the first and second stages exceeded 24 hours The prognostic importance of prolongation of the first and second stages beyond 24 hours as also of premature rupture of the membranes was analysed *Prolonged*

of the pregnancy complications The incidence of complications both during labour and the puerperium was significantly higher statistically in those patients who had had complications of any kind during pregnancy Infants born to mothers with complications during pregnancy were more frequently premature (9 9 per cent against 5 6 per cent) and were subject to a higher perinatal mortality rate (4 9 per cent against 3 6 per cent), although these differences were statistically insignificant However, the figure quoted for perinatal mortality does not give adequate statistical expression to the worsening infant prognosis implicated with maternal complications of pregnancy, since the significantly increased rate of delivery by Cæsarean section in those cases implies obvious prognostical improvement for the infants, as will be discussed below When the patients with complications of any kind during labour were compared with those having entirely uncomplicated deliveries, the perinatal mortality figures were found to be 6 3 and 2 3 per cent respectively This difference in mortality is significant ($P < 0\ 05$)

As judged from the results thus obtained, it would seem justifiable to replace Meyer's earlier subdivision of elderly primigravidæ for prognostic purposes based on presumed variations in fertility constitutions, by a classification dependent upon the presence or absence of complications during pregnancy and labour This should enable a more adequate assessment of the prognosis for both mother and child to be reached This classification also stresses the importance of intensive ante-natal supervision and care in order to achieve a generally improved obstetric prognosis for these patients

Toxæmia dominated the complications of pregnancy Toxæmia of varying degree was present in 204 cases (37 6 per cent) Eclampsia was not seen in any case in this series The incidence of toxæmia in elderly primigravidæ was exactly twice the incidence in the worst group of the total series of the department namely *all* obstetric cases aged 40 or more Comparing elderly primigravidæ with and without toxæmia during pregnancy the incidence of puerperal complications was found to be distinctly higher in the former ($P < 0\ 001$), whereas no difference could be demonstrated as regards the risk of complications during delivery of

the use of section as a prophylactic measure on behalf of the child, in primigravidæ aged 40 or more The section rate differed significantly between the highest age group and the lower groups ($P<0.001$) The percentage frequency of operative vaginal delivery was, however largely independent of the patient s age The significance of Cæsarean section in relation to the infant prognosis will be discussed further below

Table V gives the perinatal mortality and the postoperative

Table V *Perinatal Infant Mortality and Postoperative Morbidity in Mother and Child Related to Different Delivery Operations*

	Number of Infants	Perinatal Mortality Per cent	Percentage Frequency of Postoperatively Complicated Cases	
			Mother	Infant
Low forceps	44	2 3	62 6	4 0
Mid high forceps	55	9 1		
Cæsarean section	98	0	75 3	11 1
Vacuum-extraction	10	0	30	10
(Other operative deliveries	25	24)		

morbidity in mother and child related to different methods of operative delivery It is apparent that instrumental delivery is more often commenced at a higher pelvic level in elderly primigravidæ than in other obstetric cases This circumstance which was also observed by earlier writers has an unfavourable influence on the infant prognosis The perinatal mortality rate associated with mid high forceps delivery was 9 1 per cent Of course the causal connection between the surgical procedure itself and the death of the infant may well be difficult to analyse However of the perinatal mortality associated with mid-high forceps mentioned 6 per cent could be attributed mainly to cerebral damage in all probability a direct result of the method of delivery As can be seen from Table V the infant mortality associated with low forceps was considerably less (2 3 per cent) and was *nil* in the patients delivered by Cæsarean section or vacuum

labour carried an increased rate of operative delivery, mainly vaginal extractions, and an increased frequency of puerperal complications Perinatal mortality was uninfluenced by the prolongation of labour, but examination of those infants who did die revealed a higher frequency of intracranial hæmorrhage than in the other cases (50 per cent compared with 14 per cent) Of those cases which had *premature rupture of the membranes*, delivery was premature (*i e* occurred before the end of the 38th week) in 23 5 per cent (10 1 per cent in the other cases, $P<0\ 001$) To some extent this fact was due to a higher frequency of breech and twin deliveries Premature rupture of the membranes was not associated with any increase in perinatal mortality

The general prognostic significance of complications during labour was previously mentioned Equally important and interesting is the prognosis of various operative delivery methods In all 227 patients (41 8 per cent) were delivered operatively Table IV

Table IV *Distribution of Spontaneous Deliveries, Cæsarean Sections, and Other Operative Deliveries with Regard to Different Age Groups*

		35–36 Yrs.	37–39 Yrs.	≥40 Yrs.	Total
Spontaneous delivery,	number	151	128	37	316
	%	66 2	60 4	35 9	58 2
Operative vaginal delivery	number	53	55	22	130
	%	23 3	25 9	21 4	23 9
Cæsarean section,	number	24	29	44	97
	%	10 5	13 7	42 7	17 9

shows the distribution of operative and spontaneous deliveries between the various age groups It is evident that the incidence of spontaneous delivery falls markedly with increasing age, while the incidence of Cæsarean section shows a correspondingly sharp increase This is due to the principles of the department during the period analysed, namely the extremely generous interpretation of conventional maternal indications for section as well as

ciated with breech deliveries was 16 6 per cent but the difference compared with the present series was insignificant. To a large extent the high perinatal mortality is linked to the increased incidence of prematurity in these cases Thus, birthweights less than 2 500 g were noted in 40 per cent of cases as compared with 6 9 per cent in other presentations However it should also be emphasized that 14 cases, wherein a foot or breech presentation was either corrected before labour commenced or delivered by section had no perinatal mortality

Puerperium As is shown in Table 1 puerperal complications arose in 45 9 per cent of cases, the incidence in the total obstetric series of the department being significantly smaller—17 0 per cent ($P<0\ 001$) The high complication rate in the elderly primigravidæ can be ascribed to the high rate of labour abnormalities operative deliveries and the reduced elasticity of the birth canal Relatively few of the complications were serious however The median value (P_{50}) for postdelivery in patient care was 9 days as against 6 days in the total series of the department

The infant A raised incidence of prematurity (i e a birth weight <2 500 g) was observed in the infants in this series The rate of prematurity was 8 4 per cent, whereas the corresponding figure in the total series of the clinic was 3 6 per cent The difference is statistically significant ($P<0\ 001$) In the series under study there was no statistically significant difference between the three age groups as regards the frequency of prematurity It seems likely that the raised incidence of prematurity in elderly primigravidæ is particularly related to the increased morbidity during pregnancy (*cf* Raihä 1959)

In the 526 surviving infants a total of 191 complications *i e* deformities diseases and injuries arose in 169 infants a complication rate of 30 7 per cent As compared with the total series of the department this figure is raised even though the majority of complications were not serious In all 44 infants (8 0 per cent) were transferred to another department usually the pædiatric department for further treatment

Perinatal mortality In addition to the individual influence of various clinical factors on the perinatal mortality accounted for above a general view on this subject will be given In all 24 in

extraction With operative deliveries other than those mentioned, the total infant mortality figure was appreciably higher, but in these cases the prognosis for the infant was either a foregone conclusion (as in cranial perforation, for example), or else it was dependent on a complex ætiological pattern, where factors other than the procedure itself (*e g* prematurity) were of distinctly greater significance (most breech- and twin deliveries being included in this group)

The number of vacuum-extractions is too small to permit of statistical conclusions, nor is it representative of the series as a whole, since the method did not come into routine use in this clinic before 1958 However, when taken together with the additional experience gained after 1960, it is likely that vacuum extraction is superior to mid high forceps in regard to the prognosis for the child (*cf* Bergman, Malmstrom and Schöön, 1961)

The total number of Cæsarean sections was 97—a frequency of 17 9 per cent overall, although the incidence rose sharply with increasing age (Table IV) In 47 cases indications other than the age factor were present, while in the remainder the patient's age was the main indication or was a substantially contributary factor Of considerable prognostic importance was the observation that Cæsarean section incurred *no perinatal mortality* (Table V), notwithstanding that these cases included many serious complications of labour and consisted largely of patients from the highest age group The incidence of prematurity was the same as in the forceps series In contrast to the forceps cases there was an increased maternal postoperative morbidity, the complications being as a rule mild, however with insignificant effect on the mean duration of stay in hospital

Of special interest is the prognosis in *breech deliveries*, which by experience are known to carry an unfavourable prognosis in elderly primigravidæ In all 25 infants presenting by the foot or breech were delivered from 24 mothers 7 perinatal deaths occurred, a mortality of 28 per cent (24 per cent after correction for one infant with major deformities) The overall perinatal mortality for other presentations was 3 2 per cent In the total obstetric series of the department the perinatal mortality asso-

Table VI *Perinatal Mortality with Regard to Different Maternal Age Groups Overall and Corrected Figures*

Maternal Age Group	35–36 Yrs	37–39 Yrs	≥40 Yrs	Total
Number of infants	231	215	104	550
Total perinatal mortality %	5·2	4 7	1 9	4 4
excluding antenatal deaths %	3 9	3 3	1 0	3 1
Perinatal mortality premature infants excluded %	3 9	1 4	0	2 4
excluding antenatal deaths %	3 0	0 9	0	1 6

as a prophylactic measure on behalf of the child was prevailing at the department during the period of the present investigation Thus, the incidence of section in the highest age group was almost 43 per cent The percentage of operative deliveries by the vaginal route did not vary between the age groups (Table IV) As no other factors of any significance could be incriminated in this context a strong correlation between the increased use of Cæsarean section and the sharp fall in perinatal mortality (Tables IV and VI Fig 1) was suggested

General conclusions The high incidence of complications which characterises pregnancy in elderly primigravidæ has a markedly adverse effect on labour and the puerperium as well as on the prognosis for the child. For practical prognostic purposes a subdivision into cases with and without such complications would therefore seem adequate and suitable The obstetrical management should also be planned with regard to the age of the elderly primigravida In view of the frequency of complications a clear statistical border line could be drawn at the age of 40 Strongly allied with the high incidence of pregnancy complications is the raised frequency of premature infants To a great extent the situation appears amenable to improvement by intensified and specialised ante-natal supervision and care The indications for admission to hospital during pregnancy should be very liberal In particular regular admission to hospital some time before the expected date of delivery is to be recommended Com-

fants were stillborn or died before the end of the first week, corresponding to a total perinatal mortality rate of 4 4 per cent Half of these infants were delivered normally and the other half operatively If the 7 cases of fœtal death occurring prior to the onset of labour are excluded, the corrected mortality becomes 3 1 per cent The corresponding figures in the total obstetric series of the department were 2 47 and 1 75 per cent respectively, the difference between the two series being statistically significant (P<0 02)

Prematurity is one of the most important factors in this obstetric category as regards child prognosis The mortality rate in infants with a birthweight of less than 2,500 g was 26 per cent Though constituting only 8 4 per cent of the entire series, the premature infants accounted for 50 per cent of the perinatal mortality In the weight-category between 3,000 and 4,500 g (73 per cent of the series) the mortality was 1 7 per cent The incidence of prematurity in non-surviving infants rose with increasing maternal age

As was previously observed, maternal complications during pregnancy and/or labour were correlated with a raised infant mortality Of the perinatal deaths, 17 (71 per cent) were born to mothers with complications of pregnancy, and 15 (63 per cent) to mothers with complicated labour, some cases belonging to both groups In only three cases (13 per cent) were such maternal complications lacking

In sharp contrast to the total obstetric series of the department it was found that the perinatal mortality fell sharply with increasing maternal age As is evident from Table VI, this applied both to the overall figures and to those which had been corrected for prematurity and antepartum death It is quite remarkable that infants born to elderly primigravidæ, aged 40 or more, had a mortality rate even lower than that in the total series of the department, despite the high incidence of complications in the former A careful analysis of this relationship showed that the only factor to be held responsible was the varying frequency of Cæsarean section As was pointed out previously, a very liberal application of this operation in the oldest group of elderly primigravidæ, not only on conventional maternal indications but also

lactic indications on behalf of the child in 43 per cent of primigravidæ aged 40 and over, and this was instrumental in achieving a perinatal mortality lower than that prevailing at this department generally, namely 1 9 per cent overall, and nil if prematures were excluded The analysis also suggests that in those primigravidæ aged 35–39 there is a good case to be made out for a section rate of at least 15–20 per cent This presupposes, however, that these cases will be delivered in specialised departments with adequate equipment and facilities

Spontaneous delivery with a favourable outlook for the child can be anticipated mainly in those elderly primigravidæ in whom pregnancy was completely free from complications In a proportion of cases where delivery by the vaginal route seems initially to be both possible and reasonable, however, indications may often arise for instrumental extraction In this situation the vacuum extractor appears to offer a better prognosis for the infant than forceps

Of course individual judgement is always the deciding factor as regards the obstetrical management in a given case but it would at present appear that a management based on the principles mentioned would improve the poor obstetric prognosis which is characteristic of these patients and effect an infant prognosis considerably closer to that associated with the younger obstetric patient

SUMMARY

A series of 543 primigravidæ aged 35 or more and delivered at the University Clinic of Obstetrics and Gynæcology Lund during the period 1950–60 was subjected to a detailed analysis as regards factors of prognostic significance for mother and child Elderly primigravidæ create a prognostically unfavourable obstetric group particularly as regards the prognosis for the infant The present analysis suggests that this situation could be improved by intensified and specialised ante natal supervision and care a considerable extension of the use of Cæsarean section and the use of the vacuum extractor instead of forceps in those cases where vaginal extraction is indicated

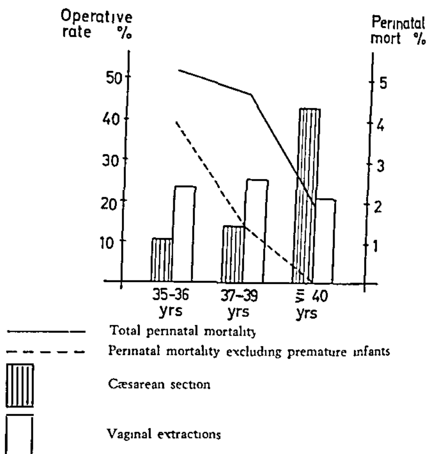


Fig 1 Perinatal infant mortality in relation to the incidence of Cæsarean section and other operative deliveries in different maternal age groups

plications found to have extremely bad prognostic significance for the child are bleeding of unknown cause during pregnancy, breech presentation, and twin pregnancy Toxæmia of any severity also renders increased supervision necessary

Labour is characterised by a high frequency of complications, partly as a result of the effects of ageing on the birth canal as well as on the body generally Any complication during labour worsens the outlook for the child Factors emerging from the analysis of various delivery methods suggest that a considerable extension of the use of Cæsarean section is at present the most promising means of reducing the perinatal infant mortality In this series Cæsarean section was performed, partly on pure prophy

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CONSTRICTION OF THE UMBILICAL CORD AS A CAUSE OF FŒTAL DEATH

BY

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Localized constriction of the umbilical cord occasionally associated with torsion, was reported in various publications in the nineteenth century

Dohrn (1861) reviewed the literature and found 85 cases of torsion of the cord. Constriction was reported in some of these cases According to Dohrn a case of torsion of the cord was first reported by Ruysch (1691) while Burdach (1758) was the first to describe the combination of torsion and constriction In addition to his extensive survey of the literature, Dohrn reported a case of constriction and torsion of the fœtal end of the umbilical cord He expressed the view that the torsion was primary to the constriction, which led to fœtal death

Cavasse (1865) also reported a case of constriction of the fœtal end of the cord but did not mention torsion He found thrombosis of the umbilical vein in relation to the constricted part and suggested that the condition was due to phlebitis of the umbilical vein extending to the surrounding structures Wharton s jelly was completely absent in the constricted part of the cord

A similar ætiology was proposed by Browne (1925) who found thrombosis of both umbilical arteries while the vein in his case was permeable although the lumen was narrow The author assumed that the condition was due to arteritis In more recent

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Fig 2 Case 1 The constricted area of the cord

reported three cases which differed from previously reported cases in that they did not exhibit a localized constriction of the cord in each case, however the cord was completely devoid of Wharton s jelly In this connection it is interesting to note that Hohl (1862) observed two cases of constriction of the fœtal end of the cord with delivery of living full term infants

In all the cases so far considered the constriction was situated in the fœtal end of the cord. Only Gaettens (1841) observed constrictions with different localization Among his seven published cases there was one with a constriction at the placental end and another revealed four strictures of the cord. Thus, typically constriction of the cord seems to be situated at the fœtal end Other sites are rare



Fig 1 Case 1 Constriction at the placental end of the cord

literature, typical cases of constriction of the fœtal end of the cord have been recorded by Edmonds (1954) and Piraux (1957) In the latter case, no torsion was detected. Novak (1958) reported a case of torsion of the cord at the same site, but did not mention any constriction Hirsch (1865) published a case of constriction and torsion of the cord of one twin In this case, the cord had been twisted off, the dead foetus lying freely in the amniotic cavity The second twin was alive Gallagher and Malone (1956) described a similar case of torsion amputation of the cord in the constricted area near the foetus Mc Clintocks case (1943) may belong to the same group, the cord having been detached near the umbilicus of the fœtus A constriction was, however, not described and, in contrast to the other cases on record, the child was born at term and the heart sounds had ceased shortly before birth In contrast to most authors, Shauta (1881) expressed the view that the torsion as well as the disappearance of Wharton s jelly occur after the death of the fœtus as a consequence of maceration The author



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Fig 3 Case 1 Transverse section of the constricted area showing thrombosis of one umbilical artery

Five cases of constriction of the cord are described below They were all seen in the Department of Obstetrics of the Copenhagen County Hospital at Glostrup during a two year period with a total of 1,369 deliveries, including 25 cases of *ante partum* fœtal death

Case Reports

Case 1 (231102) – A 37 year old para IV was admitted to the hospital 10 days before estimated date of confinement with a twin pregnancy Fœtal heart sounds were audible only from one fœtus The bag of waters had ruptured 20 minutes before admission Three hours later a living boy was delivered The birth weight was 3 050 g and the length 50 cm A few minutes later the second twin was born It was a dead, macerated male fœtus weight 1,850 g, length 46 cm Examination of the secundines disclosed two chorions The placenta and cord belonging to the first twin were normal In the second placenta numerous white infarctions were seen The corresponding cord was macerated The diameter was normal up to 2 cm from the placenta, where it was constricted, the diameter being only a few millimetres (Figs 1 and 2) Histological examination of transverse sections of the con

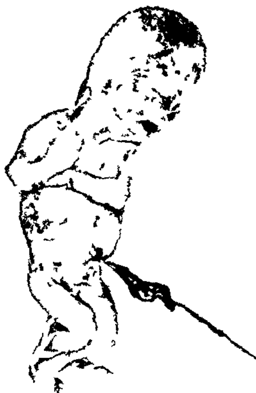


Fig 4 Case 2 Constriction at the foetal end of the cord

stricted area showed complete absence of Wharton's jelly There were two arteries one of which was completely obstructed by a thrombus (Fig 3) The other artery also contained a thrombus but the lumen was not entirely closed The vein could not be detected The vessels were surrounded by a layer of connective tissue Examination of cross sections of the remaining part of the cord revealed three dilated vessels with incipient thrombus formation

Case 2 (290806) A 35 year-old para II gravida V was admitted to the hospital in the 32nd week of pregnancy The fœtal movements had ceased two weeks previously 12 hours later a macerated male foetus was delivered weight 1 100 g, length 37 cm A few white infarctions were seen in the placenta The cord was constricted in the area near the foetus in which part Wharton's jelly seemed to be absent (Fig 4)

Case 3 (370614) A 24 year-old para II was admitted in the 28th week of pregnancy Fœtal movements had ceased three weeks previously After



Fig 5 Case 4 Torsion amputation at the fœtal end of the cord

intravenous drip infusion of oxytocin a macerated fœtus was delivered The length of the fœtus was 32 cm The placenta was small but otherwise normal A typical constriction was seen in the fœtal end of the cord

Case 4 (380228) – The patient was a 23 year-old para I, gravida II who was seen in the 32nd week of pregnancy the fœtal movements had ceased two weeks earlier On admission, no fœtal heart sounds were audible After 8 hours labour a macerated male fœtus was delivered The weight was 1,600 g and the length 42 cm There was 3 000 ml of amniotic fluid The fœtus had multiple malformations The placenta was normal The cord was constricted at the fœtal end and was here completely twisted off (Fig 5) 5 cm nearer to the placental end of the cord another constriction was seen (Fig 6) Histological examination of the cord showed absence of Wharton s jelly, and the vessels were surrounded by connective tissue

Case 5 (281028) – The patient was a 33 year old para IV, who was admitted in early labour in the 30th week of a twin pregnancy Four hours later a macerated male fœtus was delivered weight 970 g length 35 cm



Fig 6 Case 4 A second constriction is seen nearer to the placental end of the cord

The second twin was delivered alive weight 1 100 g, length 36 cm Examination of the secundines showed one chorion The placenta was the site of a few white infarctions The cord belonging to the second twin was normal whereas a constriction was seen in the fœtal end of the cord belonging to the dead fœtus Histological examination of the latter cord showed two intact arteries The lumen of the vein was narrow with damaged endothelium but without thrombosis The vessels were surrounded by connective tissue but no Wharton's jelly was present

Discussion

Constriction of the umbilical cord has been reported in 13 cases in the last century Few authors have seen more than one case

Nevertheless the present series suggests that the condition is probably not very uncommon This assumption is also supported by the fact that 85 cases could be traced in the literature up to 1861 Among these cases are some in which only a torsion of the cord is reported although they probably belong to the same group The present five cases illustrate most of the known variations of this anomaly Thus, the series includes one case of constriction of the placental end of the cord, which has been reported in only one previous case (Gaettens, 1841) In the remaining four cases, the constriction was situated at the fœtal end, which is the typical location In one of our cases two constrictions were present. In two cases the anomaly was found in twin pregnancies and resulted in the death of one fœtus, while the other was born alive The twins were monochorionic in one case and dichorionic in the other Finally, one case revealed a torsion amputation of the cord

Some authors describe both constriction and torsion of the cord, while others only mention torsion In fact, it is very difficult to make sure of the existence of an intra-uterine torsion of the cord except in the cases in which the cord is twisted off It is likely that most cases of constriction are associated with torsion of the cord

It has been claimed that both constriction and torsion of the cord occur after the death of the fœtus caused by the maceration which commences at the fœtal end, in which the oxygenation from the placenta first ceases (Edmonds) This theory is probably erroneous for the following reasons The constriction may be seen in the placental end of the cord as illustrated by one of the cases reported here, although this site is uncommon Secondly, deliveries of living infants have been recorded in cases of constriction of the cord Moreover, most cases of maceration of the cord are not accompanied by constriction It therefore appears most likely that the constriction is present before the death of the fœtus However, the torsion may presumably continue after the fœtal death as a result of the uterine contractions giving rise to changes in the position of the dead fœtus

Lack of Wharton s jelly in a segment of the cord will expose it to torsion caused by the fœtal movements In this way, the blood circulation, probably already reduced by the stricture, will

be completely interrupted Thrombosis of the vessels of the constricted area indicates that the circulation has been reduced before the lethal torsion After the death of the fœtus the continued torsion may result in complete torsion amputation of the macerated cord It cannot be excluded that the cord may be twisted off while the fœtus is still alive and thus cause its death

The cause of the constriction is unknown It may be a maldevelopment of Wharton s jelly, i e a congenital malformation Another possibility is that Wharton s jelly disappears as a consequence of degeneration Cases of mucoid degeneration of Wharton s jelly were described by Bergman, Lundin, and Malmström (1961)

Although the anomaly obviously is not amenable to antenatal diagnosis or therapeutic measures, it is of interest to elucidate the cause of fœtal death in such cases Repeated cases have not been described and consequently the prognosis for subsequent pregnancies is favourable

SUMMARY

Localized constriction of the umbilical cord in five cases of fœtal death is described It is suggested that the death of the fœtus is caused by torsion of the constricted area

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THE EFFECT OF PROSTAGLANDIN E_1 ON THE HUMAN UTERUS AND THE FALLOPIAN TUBES IN VITRO

BY

F SANDBERG A. INGELMAN SUNDBERG AND G RYDÉN

In a previous paper (Sandberg *et al*, 1963) the effect of "prostaglandin" an extract from human semen prepared according to Eliasson (1959), was tested on human Fallopian tubes *in vitro* This preparation exerted a specific action on the tubes as demonstrated by an increase in tonus and amplitude maximum in the proximal part and the reverse effect on the rest of the organ

Bergström *et al* (1960 1962) have recently shown that the biological activity of the prostaglandin extracts of sheep vesicular glands is due mainly to three related compounds, Prostaglandin E E_2 and E_3 (PGE, PGE_2 and PGE_3) and PGE_1 has also been found to occur in human seminal fluid (Bergström and Samuelsson, (1962)

Prostaglandin E_1 has the structure shown below and PGE_2 and PGE_3 have one and two additional double bonds respectively Reduction of the keto group in each case yields a pair of isomeric alcohols (PGF and PGF) which also are biologically active (*cf* Bergström *et al* 1962)

It was therefore of interest to compare our results obtained by using *Eliasson's* "prostaglandin" preparation with the effects of prostaglandin E_1 (PGE_1) one of the main active components in chemically pure form In order to obtain an integrated picture

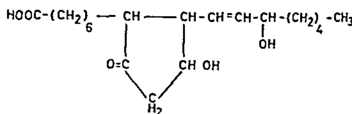


Fig 1 Prostaglandin E_1 2-(6-carboxy hexyl) 3 (3 hydroxyoctan 1 yl) 4 hydroxy-cyclopentan 1 one

of its action on the human female genital tract, prostaglandin E_1 was tested both on the uterus and on the Fallopian tubes The substance was kindly supplied by Professor S Bergstrom, Stockholm

Material and Methods

The Fallopian tubes were obtained from 33 patients at the time of hysterectomy Only tubes with macroscopically normal appearances were used The classification was based on the case history and correlated with the assessment of the cyclic phase of the endometrium The patients were classified in three groups

(1) *Proliferatory group* patients with normal menstrual cycle and normal endometrium in the proliferatory phase

(2) *Secretory group* patients with normal menstrual cycle and normal endometrium in the secretory phase

(3) *Post-menopausal group* patients who had not menstruated for at least one year

The myometrial tissue was obtained from 21 patients operated upon because of fibroids Muscle strips were cut longitudinally

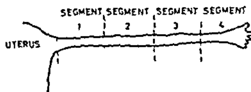


Fig 2 Definition of the different tubal segments

from the corpus and transversally from the isthmus The classification was the same as for the tubes

Method

The motility of the longitudinal musculature of the Fallopian tubes and of the uterine muscle strips was studied using a modified Magnus Kehrer technique as described earlier in this journal (Sandberg *et al* 1960) Immediately following the operation the tubes were immersed in Ringer solution After removal of the peritoneal covering the tube was divided into four parts of equal length The proximal part was numbered segment 1 and the most distal one (the infundibular) segment 4 (*cf* Fig 2) For estimation of effects six parameters were considered and statistically analyzed using Student's t test (Sandberg *et al* 1960)

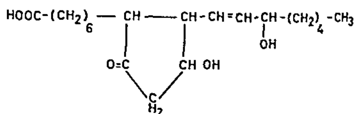


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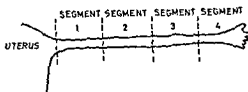


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Table I *In vitro Effects of Prostaglandin E_1 Tested on the Longitudinal Musculature of the Fallopian Tube from 26 Women of Fertile Age The Tubal Segments Defined as Shown in Fig 2*

Parameter		Segment 1	Segment 2	Segment 3	Segment 4
Incidence of response		56/67 =84 %	50/60 =83 %	65/83 =78 %	50/69 =73 %
Change of motility pattern %		14	44	26	20
Tonus	increase %	63	6	3	2
	unchanged %	20	50	31	30
	decrease %	17	44	66	68
Frequency	increase %	27	4	7	4
	unchanged %	54	32	50	40
	decrease %	19	64	43	56
Amplitude	increase %	14	6	16	8
	unchanged %	38	30	26	38
	decrease %	48	64	58	54
Amplitude max	increase %	57	6	5	2
	unchanged %	5	8	11	8
	decrease %	38	86	84	90

Results

I *Fallopian Tubes*

The results concerning the effects of prostaglandin E_1 in the proliferatory, secretory and postmenopausal groups are given in Tables I–II Since no differences in response could be found between tubes in different sexual phases, the results obtained in the proliferatory and secretory groups have been listed together in Table I

Prostaglandin E_1 produces different responses in the proximal and the distal part of the tube In the proximal part (segment 1) prostaglandin E_1 causes a stimulatory effect, demonstrated by an increase in tonus and amplitude maximum, whereas it has an inhibitory effect in the rest of the tube (segments 2–4), shown

Table II *In vitro Effects of Prostaglandin E_1 Tested on the Longitudinal Musculature of the Fallopian Tube from 7 Post Menopausal Women The Tubal Segments Defined as Shown in Fig 2*

Parameter		Segment 1	Segment 2	Segment 3	Segment 4
Incidence of response		18/21 =86 %	16/20 =80 %	13/20 =65 %	5/15 =33 %
Change of motility pattern %		6	0	23	0
Tonus	increase %	78	44	0	0
	unchanged %	16	31	0	0
	decrease %	6	25	100	100
Frequency	increase %	16	12	0	0
	unchanged %	56	57	92	80
	decrease %	28	31	8	20
Amplitude	increase %	11	6	8	0
	unchanged %	39	50	38	40
	decrease %	50	44	54	60
Amplitude max.	increase %	78	50	0	0
	unchanged %	11	6	8	0
	decrease %	11	44	92	100

by a decrease in tonus and amplitude maximum. In the post menopausal group however the tonus and the amplitude maximum are increased in segment 2 also

The typical effects of prostaglandin E_1 on the different segments of the Fallopian tube are illustrated in Fig 3

II *Uterus*

The results obtained are listed in Table III Prostaglandin E_1 exerts an inhibitory effect on the uterus This is shown by a decrease in all parameters in the corpus In the isthmus, however the tonus remains unchanged The inhibitory effect on the tonus in the corpus is most pronounced in the proliferatory phase, otherwise no differences in response in the different sexual phases can be demonstrated Typical responses are shown in Fig 4

Table III *In vitro Effects of Prostaglandin E_1 Tested on Musculature of Corpus and Isthmus from 21 Women of Fertile Age*

Parameter		NONPREGNANT UTERUS			
		Corpus		Isthmus	
		Prolif	Secr	Prolif	Secr
Incidence of response		47/56 =84 %	23/34 =68 %	29/29 =100 %	16/20 =80 %
Change of motility pattern %		38	26	76	56
Tonus	increase %	0	0	0	0
	unchanged %	15	57	73	75
	decrease %	85	43	27	25
Frequency	increase %	11	0	0	0
	unchanged %	36	13	7	19
	decrease %	53	87	93	81
Amplitude	increase %	4	4	0	6
	unchanged %	19	13	3	12
	decrease %	77	83	97	82
Amplitude max	increase %	0	4	0	6
	unchanged %	4	4	3	6
	decrease %	96	92	97	88

Prostaglandin E_1 was not tested on uteri of post-menopausal women

Discussion

From the results obtained it is evident, that postaglandin E_1, when tested *in vitro*, exerts a stimulatory action on the proximal part of the tube, whereas its effect on the rest of the oviduct and on the uterus is inhibitory In Fig 5 this effect on the tube is illustrated for the tonus The observation, that in the post menopausal group segment 2 shows almost the same response as segment 1, might be explained by a more pronounced age atrophy

of distal part

E_1 is resorbed and transported to the uterus and the tubes, where it exerts its specific action The relaxation of the uterus causes a passive suction of cervical secretion into the uterine cavity, facilitating the transport of the spermatozoa

The contraction of the proximal part of the tube in combination with a simultaneous relaxation of the rest of the organ causes a suction, favouring the entrance of the ovum from the abdominal *cavity into the tube*, and its retention in the middle part of the oviduct The contraction of the proximal part of the tube probably offers no hindrance for the active penetration of the spermatozoa into the tube

In preliminary experiments Asplund (1947) was able to demonstrate that intravenous administration of prostaglandin, extracted from human semen, according to v Euler (1939) caused a clear and fairly protracted lowering of the tonus of the abdominal tubal ostium in rabbits This observation is in accordance with our findings on human tubes *in vitro*

In contrast to the observations of Eliasson and Posse (1960) in human *in vivo* experiments on the uterus we have found a pronounced inhibitory effect of prostaglandin in all sexual phases (menstruation not tested) *in vitro*, both with prostaglandin E_1 and Eliasson s preparation of prostaglandin

SUMMARY

Using Magnus Kehrer s technique the effect of prostaglandin E has been investigated on different parts of human Fallopian tubes from 33 women and on corpus and isthmus of the uterus from 21 women

Prostaglandin E_1 exerts a specific action as demonstrated by an increase in tonus and amplitude maximum in the proximal part of the tube and the reverse effect on the rest of the tube and on the uterus No difference in response to prostaglandin F of tubes from different sexual phase is observed

A hypothesis for the action of prostaglandin E_1 during the process of fertilization is presented

Acknowledgements

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SIZE MEASURING AT LAPAROSCOPY

BY

ALF SJÖVALL

The techniques of peritoneoscopy, comprising culdoscopy and laparoscopy through the anterior abdominal wall, rank among the foremost diagnostic aids in gynæcology

In many centres one or both belong to the daily routine In others surprisingly enough they are considered time consuming cumbersome or even dangerous

In our Department peritoneoscopy has been used since 1948 with increasing frequency In over 700 laparoscopic examinations in gynæcological patients complications were few (1 2 per cent) never serious and without mortality

Peritoneoscopy has added enormously to the accuracy and swiftness of diagnosis It is time saving for both patient and hospital as early diagnosis often precludes the need for a period of observation and expectant treatment It also renders superfluous other diagnostic procedures such as X ray examination

For practical reasons we generally nowadays prefer laparoscopy through the anterior abdominal wall and only occasionally, for instance in very fat patients do we perform culdoscopy

After bimanual examination under general anaesthesia—as a rule an essential step in obtaining diagnostic information—the alternatives of immediate operation or laparoscopy pending a final decision are considered As ours is a teaching hospital examination under anæsthesia is preferred as it provides an opportunity for several students to examine bimanually without inconvenience to the patient The findings on palpation are immediately checked

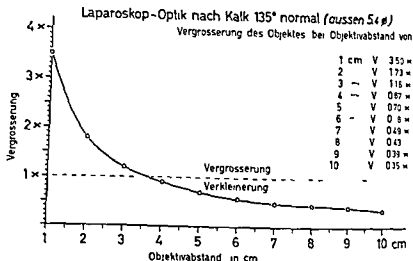


Fig 1 Magnification variation at laparoscopy (by kind permission of professor Kalk)

at subsequent laparoscopy and/or laparotomy The procedures are thus in many instances carried out at one and the same session and no time is wasted

At laparoscopic examination there is the optical difficulty that magnification varies with the distance between the distal lens of the laparoscope and the object being viewed in the abdominal cavity With the Kalk & Heynemann instrument *magnification* is 3 5× at a distance of one centimetre On the other hand, at a distance of, for instance, 10 centimetres the object is seen in miniature, being *diminished* to 0 35 of its actual size (Fig 1)

It is of course possible to make an approximate size-estimate of what is seen by comparison with organs or structures of known size, such as the body of the uterus Experience from laparotomies done immediately after laparoscopy has, however, taught us that one is often mistaken

No special device for accurate size measuring at laparoscopy has, as far as the writer knows, appeared in the literature The solution, however, is simple and obvious

If a graduated trocar-needle is inserted into the abdominal cavity close to the object the size of which is to be estimated, the distance obviously does not matter at all Dimensions are read off directly on the graduated needle In essence this is the same as placing a measuring-tape alongside an object to be photographed,



Fig 2 The measuring needle instrument inserted

the use of a measuring rod when taking X rays for pelvimetry or the object micrometer for microscopy

Consequently a blunt graduated needle has been manufactured for this purpose The needle is introduced into the abdominal cavity through a special trocar cannula inserted through the ab dominal wall beside the laparoscope after removing the cannula stylet (Fig 2) The cannula is 26 cm long its gauge 2 mm The blunt needle is 35 cm long and graduated in centimetres (Fig 3) The needle is placed alongside the object to be measured and its dimensions are read off (Fig 4) Measurements at subsequent laparotomy have shown the assessments to be correct

It is sometimes better to use not the needle but a ureteric ca theter which sweeps more easily over undulating surfaces

The measuring needle instrument can be used in many other ways for which several instruments have been devised earlier by others (Kalk Palmer Sjostedt and others) the first by the inventor of laparoscopy Kelling (1910)

Organs and structures may be manipulated with the needle their consistency felt and structures obscuring the visual field

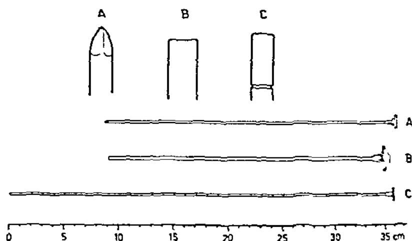


Fig 3 The measuring needle, trocar-cannula and stylet.



Fig 4 Laparoscopic photograph measuring a small ovarian cyst of 5 cm diameter

pushed away Aspiration of peritoneal fluid puncture, biopsy and diathermy can be done through the trocar cannula

SUMMARY

A simple instrument for measurement of the size of intraperitoneal organs and structures at laparoscopy is described

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HYSTEROSCOPY THROUGH A TRANSPARENT RUBBER BALLOON IN PATIENTS WITH CARCINOMA OF THE UTERINE ENDOMETRIUM

BY

TORSTEN SILANDER

In Sweden about 6 per cent of all female carcinomata originate in the corpus uteri The results following the treatment of carcinoma corporis are dependent upon the spread of the tumour in the endometrium and the penetration into the muscular wall If the treatment can be individually planned according to the circumstances, better results will be obtained In order to evaluate the spread in the endometrium fractional currettage and hysterography (Norman, 1950) have been tried

Experience gained at the Radiumhemmet, Stockholm, demonstrates, however, that diagnostic difficulties are often encountered in the individual case

I have therefore investigated the possibilities of using a new hysteroscopic method to get a more accurate picture of tumour spread The object of the investigation was also to ascertain whether this hitherto experimental method would have routine clinical application

Earlier Investigations

The failure to explore the uterine cavity satisfactorily has long stimulated attempts to find a method for direct visual inspection of the interior of the organ The first steps taken in this direction

deserve to be mentioned as a matter of interest In 1864 Aubinais tried to apply what he called 'l'uteroscopie' in a pregnant woman The examination was carried out in connection with the delivery The woman's abdomen was covered with closely fitting black paper sheath in which a hole was cut on either side In one hole was placed a light source, as powerful as possible, while the examiner tried to inspect the fœtus through the other opening The fœtus was discernible only as a blurred shadow Neither was it possible to see the anatomic details of the fœtus more clearly by viewing it via the vagina

In 1865 Desormeaux introduced the first endoscope that actually permitted inspection of a cavity located at a distance from the body surface The instrument consisted of a straight tube with an external lighting device and of such a fine calibre that it could easily be inserted into the cavity The construction of this endoscope marked a considerable advance, but contemporary workers did not realize its full importance Desormeaux had designed his instrument for examination of the bladder and the urethra, and it was only some time later that surgeons tried to apply the method to visualize the uterine cavity

Pantaleoni (1869) was the first to succeed in inspecting the uterine cavity in a living human subject by means of an endoscope similar to that used by Desormeaux Therapy resistant bleeding in a 60 year old woman gave him the incitement to use hysteroscopy This enabled him to discover the presence of a polypoid vegetation in the corpus Moreover, he was able to cauterize the growth with silver nitrate Pantaleoni employed this method with equal success in a further three cases His followers, however, did not obtain the same good results when applying his method In 1894 Morris reported on his not very comprehensive attempts at hysteroscopy, and in 1895 Bumm described the results of a series of intra uterine endoscopic examinations By direct inspection he was able to diagnose such conditions as endometritis, carcinomas and other tumours in the corpus However Bumm called attention to the difficulties met with because of bleeding which obscured the view Furthermore, one patient developed salpingitis following the examination

In 1908 David published a paper on hysteroscopy He de-

scribed a new hysteroscope consisting of an outer tube with a mandrel After insertion of the instrument the mandrel was replaced by an inner tube, with a lens at either end and a lamp near the eyepiece Instruments of varying length and calibre designed to suit anatomical variations in size and length and degree of cervical dilatation enabled him to perform the examination without anæsthesia A detailed report on previous investigations, indications, contra-indications and clinical application of the method without complication in 25 cases was also presented In 1914, Heineberg published an account of the hysteroscopic method which, in principle, has been generally employed ever since He described an internally illuminated endoscopic tube with a water irrigating system surrounding the inner opening The purpose of the water system was to wash away obscuring blood About twenty examinations had been performed with the instrument, mostly with satisfactory results, but in some cases the examination had been impeded by bleeding or the flexion of the uterus In these examinations general anæsthesia had been administered, but the author declared that he intended to use local anæsthesia in subsequent examinations The method had been used to diagnose endometritis and to locate residual products after abortion The need for a hysteroscopic method was strongly emphasized and illustrated by two cases which had been erroneously diagnosed after examination by conventional methods Certain important contra-indications, *e g* acute infection and, of course, pregnancy were noted

In his paper of 1925 Rubin demonstrated the inconsistency between the rapid development of cystoscopy after Nitze's description of the cystoscope (1879) and the obvious failure to establish hysteroscopy as a routine diagnostic method He ascribed this failure to two characteristic features of the uterus, *i e* the slit-shaped cavity, with the uterine walls practically in apposition, and the readiness with which the endometrium bleeds on contact with any instrument Both these characteristics involve obstacles to endoscopic examination To overcome these disadvantages Rubin first tried an arrangement in which water was irrigated over the objective by means of negative pressure He regarded the use of positive pressure as entirely contra indicated for this purpose As

satisfactory results could not be obtained with the water system he tried instead to inflate the uterus with carbon dioxide He obtained better results with this method, and in the majority of cases he succeeded in completing the examination In the cases in which bleeding occurred the examination had to be discontinued Forty two cases were reported, of which 35 were out patients and 6 in patients As a rule, the examination was performed without anæsthesia and was well tolerated, due mainly to the fine calibre of the endoscope In 8 cases the examination failed In two cases the failure was due to cervical stenosis, in the others to obstructive bleeding The instrument used was a modified cysto urethroscope, and the carbon dioxide was supplied from a syringe connected to the instrument Definite contra indications to the examination were reported In some cases, the insufflated gas caused pneu moperitoneum with slight discomfort to the patient

In order to provide a means of inspecting even a bleeding uterus, Seymour (1926) designed an endoscope, resembling a bron choscope The instrument was made in two sizes, one 6 and the other 9 mm in diameter Along the length of the instrument were arranged three channels In one channel there was a replaceable tubular light Continuous suction was maintained through the other two channels Seymour explained that the suction could keep blood away from the lamp and the objective, thus enabling him to inspect the uterine cavity However, since the field of vision was limited, the examination had to be done in stages Fifteen anæsthetized patients were examined in hospital

In 1927 von Mikulicz-Radecki and Freund presented an account of their experiences with hysteroscopy They used a water rinsing system to keep the objective clean Saline solution was admitted through an inlet tube and discharged through an outlet tube It was considered purposeless to try to keep the uterine cavity dilated by means of a liquid, because the liquid would mix instantly with blood and prevent inspection of the uterine wall Attempts were made at catheterization of the Fallopian tubes, and biopsies were made under direct vision The examinations were performed on 50 anæsthetized hospital in patients

Gauss (1928) was able to obtain satisfactory visualization of the uterine cavity by means of an optical instrument into which

a *flow* of liquid was directed from a height of 50 cm The out flowing liquid was drained into a receptacle General anæsthesia was administered to nulliparæ, but multiparæ were not generally anæsthetized No mention was made of the calibre of the instrument A right-angled objective was used The author remarked that hysteroscopy would find wide application, and mentioned that the possibility of producing tubal occlusion by intra uterine cauterization of the tubal orifices under direct vision had been discussed

Gauss' work was carried on by his co worker Schrœder, who published a report (1934) on experiences gained in 350 hysteroscopic examinations His instrument was a modified version of the hysteroscope used by Gauss The main improvement was that the lens was prograde, which greatly facilitated the examination All previously described instruments had had a right angled objective Schrœder demonstrated that there had to be the greatest possible distance between the objective and the uterine wall if it was to be accessible for inspection For this purpose, the cavity was filled with liquid from a height of 650 mm above the patient

Measurements showed an increase in intra uterine pressure to 25 to 35 mm Hg To make sure that there was no escape of liquid into the abdominal cavity, the examination was carried out with a coloured liquid at a height of 950 mm on patients on whom laparotomy was to be performed The pressure recorder used with the instrument indicated an intra-uterine pressure of 30 to 35 mm Hg in these cases In the three cases so examined no traces of the blue-coloured liquid could be discovered in the abdominal cavity during the subsequent laparotomy In order to determine what pressure was required to force liquid out through the tubes, pressure measurements were made during hysterosalpingography, using a contrast medium which had been diluted to the viscosity of water In all cases examined, the intra uterine pressure varied between 55 and 70 mm Hg On the basis of these investigations the author declared that there was no danger of liquid being forced out into the abdominal cavity when using his technique for hysteroscopy The question whether hysteroscopy was to be regarded as an essential or desirable method was answered clearly

in the affirmative, especially considering the difficulties otherwise encountered in diagnosing submucosal fibroids As Schrœder s instrument was only 8 mm in diameter, it required such a slight degree of cervical dilatation that examination of multiparæ could be performed without anæsthesia Nulliparæ were given local anæsthesia General anæsthesia was very seldom required When bleeding obscured the view, a few drops of 1/1000 adrenaline solution were added to the rinsing liquid Studies on the phases of the uterine mucous membrane were made and illustrated by pictures In two cases attempts were made at intra uterine tubal occlusion without success The failure was said to be due to the high regenerative power of the tubal mucous membrane The need for hysteroscopy in gynæcology was emphasized The author declared that, so far as submucosal fibroids were concerned, hysteroscopy could replace both digital palpation of the uterine cavity and hysterography

Schack (1936) tried to use the method described by Schrœder, but obtained quite different results He examined 50 patients, strictly following Schrœder s directions General anæsthesia was administered, execpt in one case The height of the rinsing liquid source was generally 650 mm, but had to be increased to 800 or 1000 mm when bleeding occurred In two cases, traces of a coloured contrast medium which had been added to the rinsing liquid were discovered in the abdominal cavity *Thus it was demonstrated that liquid could be forced out into the abdominal cavity under the usual conditions of hysteroscopy* Schack doubted very much whether it would be possible to keep the uterus dilated by means of the fluid pressure previously applied On the contrary he considered that it would be advantageous to allow the liquid escape as quickly as possible Satisfactory visualization was obtained in only 21 of the 50 cases examined and in most of these ca es the cervix had been dilated to about Hegar 10 As the rinsing liquid flowed out at the side of the instrument, an increase in the flow velocity was obtained The same results were attained in cases with abortion residues in which the cervix was dilated before the examination

Schack observed that if the uterine cavity could really be dilated like the urinary bladder in cystoscopy, the problem of

hysteroscopy would be solved He ascribed the repeated failure of his experiments to the occurrence of obscuring bleeding, which remained unaffected by the rinsing liquid even with the addition of adrenaline

Segond (1934) described a hysteroscope of the same type, i e with a water-rinsing system in which the calibre of the outlet was greater than that of the inlet By means of this instrument, the calibre of which corresponded to Hegar 10, Segond was able to perform intra-uterine biopsies In 3 subsequent papers, Segond gave an account of the results obtained in clinical application of the hysteroscope The results were said to be entirely satisfactory (1935, 1936, 1937)

In a series of articles between 1942 and 1957 Norment described his experiences of hysteroscopy and hysterography In 1957, he published a summary of these articles At that time, his instrument had been in process of development for 18 years In these experiments, he had occasionally used an instrument with an inflatable ruber tissue bag over the objective to keep the uterus dilated *The rubber bag was transparent and permitted* examination of the uterine cavity in some cases, but it was evidently of inferior quality, as it was not considered entirely satisfactory In some cases, the thin rubber bag became wrinkled and rendered direct inspection impossible After using this method for a few years, Norment abandoned it and replaced the rubber bag by a piece of transparent plastic However, since it was impossible to keep the lens free from blood and secretion, he was still unable to carry out satisfactory examination For the following ten years, he used a water-rinsing system which functioned satisfactorily The lens was prograde A later version of this instrument was equipped with a resecting loop for resection of endometrial polyps and submucosal fibroids On the whole, the instrument used by Norment in a great many examinations is somewhat the same as those previously employed, comprising a water system with the inflowing liquid under pressure and a free outflow from the instrument His lack of success with the inflatable rubber bag was evidently due to technical difficulties In a publication in 1955 he emphasized the value of hysteroscopy in his study of 100 patients He demonstrated the limitations of hysterography and emphasized

that this technique only demonstrated filling defects in the uterine cavity Endometrial hyperplasia may produce hysterographic appearances suggestive of polyps, submucosal fibroids or endometrial carcinoma, whereas hysteroscopy enables an exact diagnosis to be made in such cases In consequence hysterectomy may be avoided in many patients where an exact diagnosis could not formerly be made Thus, 50 out of his 100 patients had endometrial hyperplasia which required only curettage In 20 of these the hysterographic appearances suggested the presence of submucosal fibroids or polyps, but these conditions were in fact only present in 7 cases

Hysteroscopy also revealed abnormalities not suspected on clinical examination Out of 25 patients in whom submucosal fibroids were visualised at hysteroscopy, palpable tumours were present in only 18 Endometrial polyps were seen in 14 patients and in many previous curettage had been negative

In 1957, Englund, Ingelman Sundberg and Westin presented a report on a clinical study of the results of 165 hysteroscopic examinations, successfully performed with a McCarthy panendoscope The diagnosis made by hysteroscopy was accurate in 93 per cent of the cases A comparison between hysteroscopy and hysterography in a smaller group of patients favoured hysteroscopy One case, in which excessive water pressure had been applied, developed post operative salpingitis In two other cases, a rise in temperature to 38°C without any signs of salpingitis was observed

Present Investigation

Method

The method used is a development of the technique for hysteroscopy described by Silander (1962), which was based on model experiments and on uterine preparations This technique had been devised from a method for inspection of blood filled cavities described by Carlens and Silander (1961) It seemed to fulfil the basic requirements for endoscopy of the uterine cavity, *i e* capacity to keep the cavity dilated and prevention of bleeding from vascular and easily traumatized surroundings

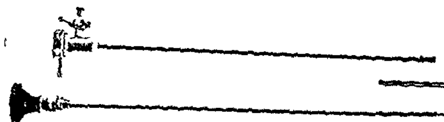


Fig 1 The Silander hysteroscope in its three component parts The letters refer to the description of the instrument in the text.



Fig 2 The outer tube placed over the telescope and locked into position with water tight closure The rubber balloon rolled on the distal part of the outer tube and locked in position by a metal ring

The instrument employed* consists of an outer tube of thin stainless steel, 7 mm in diameter, containing a telescope with a fore-oblique objective The union between the telescope and the outer tube is water-tight A cock for Luer-Lok syringes is fitted to the proximal end of the outer tube

Figs 1–4 show the appearance of the instrument which is made up of three parts

a) a telescope
b) an outer tube
c) a transparent rubber balloon

* The instrument has been manufactured by AB Stille Werner Stockholm, Sweden, and Richard Wolf, Knittlingen, Germany



Fig 3 A syringe is mounted in the Luer Lok valve fitting The balloon has been expanded by the injection of a small amount of clear fluid

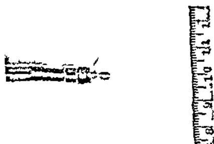


Fig 4 Detail of the expanded balloon showing it to be as transparent as a dew drop

The telescope (a) is 5 mm in diameter It is provided with a fore-oblique objective (160°) An electrical bulb is placed in front of the objective The connection between the telescope and the outer tube (b) provides a water tight seal A cock with fitting for Luer Lok syringes is located next to the occular Liquid injected through the cock is conveyed through the space between the telescope and the outer tube to the distal end of the outer tube A thin rubber balloon (c) is slipped over the lamp the objective and the conical distal end of the outer tube, where it is secured in position

by means of a metal ring The ballon is 5 mm in diameter Even *when it is only slightly distended it is completely transparent*

When the instrument is assembled, the desired amount of liquid can be injected into the balloon by means of the syringe connected to the cock near the occular

The outer tube and the syringe are sterilized by boiling The rubber balloon and the telescope are sterilized with ethylene oxide

The patient is prepared for hysteroscopy in the same way as for curettage After cleaning the vulva and vagina a speculum is inserted and the portio is gripped with a pair of forceps, so applied that they do not enter the external cervical os where they may damage the rubber balloon After determination of the depth and *position of the uterus, the cervix is dilated to Hegar 7 or 8* Then the hysteroscope with the collapsed balloon is introduced, the lamp is lighted, an adequate amount of liquid is injected into the *balloon* by means of the syringe, and the examination *is* commenced Generally, from 6 to 12 ml saline solution is sufficient to fill the cavity completely and to keep the uterine walls separated In cases in which the uterine cavity is very large, up to 16 ml may be required

In most cases, the examination is started with inspection of the internal cervical os, which is easily accessible for examination *When the objective is kept on a level with the internal os,* slight pressure on the syringe is sufficient to keep the cavity completely distended, so that the entire uterine cavity as well as the two tubal orifices are visible at the same time For closer inspection of interesting areas, the instrument is moved nearer to the uterine wall The instrument can be easily moved in all directions inside the rubber balloon The degree of dilatation of the uterus can be varied *as required by* varying the pressure exerted on the syringe In order to obtain the best possible results the cock of the syringe should not be closed during the examination The balloon follows exactly the contour of the uterine wall, and even soft growths, which could be expected to be compressed by the pressure applied, can be closely observed By varying the pressure in the balloon, it is possible to study folds in the mucous membrane and small polyps The plicæ palmatæ in the cervix are easily distinguishable, but can be smoothed out by increasing the pressure in the balloon

Since dilatation to Hegar 7 or 8 is quite sufficient, the discomfort caused to the patient is very slight and the examination may be carried out without general anæsthesia In some cases, local anæstheisa may be given

Material

The patients studied comprised 40 women whose ages varied between 32 and 72 Several weeks before admission, all these patients had undergone curettage in different hospitals and had been referred to Radiumhemmet because of suspicion of cancer of the uterine body Hystero.copy was performed prior to intrauterine exploration and, in most cases, again after careful fractional curettage The cervix was dilated to Hegar 7 or 8

Course and Result of the Examination

The examination did not fail in any of the cases studied, and a very good view of the uterine cavity was obtained No complications occurred In spite of the radium therapy, no post-operative rise in temperature above 38°C was observed There was no postoperative salpingitis Existing tumours were easily identified, and their extension could be accurately determined Most of the tumours were papillomatous with irregularly ulcerated cauliflower like excrescences In some cases, the tumour had the appearance of a mat of flat white glistening growths The microscopic examination showed that these tumours consisted of poorly differentiated carcinomas, whereas the papillomatous tumours were moderately or highly differentiated The observations made in the hysteroscopic examinations corresponded exactly with the results of the fractional curettages In some cases, the hysteroscopic examination revealed minor tumour like excrescences near the tubal orifices It proved rather difficult to reach these excrescences with instruments Because of the hysteroscopic picture a minute examination of the areas in question was made and small pieces of the growth were removed which, histologically, were of a carcinomatous nature It was po sible to determine the extension of the tumours and the border line between the tumour and normal tissue was

clearly visible In no cases of corpus carcinoma examined had the tumour reached the internal os but had extended quite close to it in 4 cases In 3 cases, coincident myomas were discovered, causing deformities in the cavity In these cases, the pressure in the balloon had to be increased to separate the uterine walls, and the presence of a myoma was already suspected when the balloon was inflated prior to inspection

In all cases examined, normal structures such as the internal os, the tubal orifices and the normal parts of the mucosa were identified

In one case, no tumour could be discovered by hysteroscopic examination The diagnosis of cancer had been arrived at after a previous curettage Renewed curettage gave no representative material The patient was given radium treatment because of the results of the previous curettage Three weeks later, a repeat hysteroscopic examination revealed a proliferation of the mucous membrane near one tubal orifice When examined microscopically, the tissue was found to be free from cancerous vegetation

In one case, a tumour was discovered in the left part of a bicornuate uterus, whereas the right half had a normal appearance These observations were helpful in the subsequent radium therapy

Inspection after curettage could be performed without difficulty and unimpeded by the bleeding resulting from the curettage In one case of cancer of the cervix, ulceration in the cervical canal was noticed in addition to the visible change of the portio

Discussion

The present investigation was started in order to ascertain the clinical applicability of the method previously used in model experiments

A similar method for hysteroscopy was described by Norment in 1943 He used a rubber tissue bag over the objective This rubber bag was evidently not quite well adapted to the purpose intended On occasions, particularly in small uterine canals, wrinkling of the bag occurred, and it was difficult to get a clear view of the cavity This drawback, which evidently made Norment

abandon his method, is not associated with the instrument used in this investigation When collapsed, the rubber bladder lies flat against the instrument The rubber balloon is shaped like a tube, 5 mm in diameter, of uniform wall thickness and closed at one end The inflatable balloon fulfils the requirement laid down by several authors, a o Rubin (1925, 1956) and Schack (1936), i e it is capable of keeping the uterine cavity dilated so that it is accessible for inspection Furthermore, the rubber balloon permits direct inspection even of a bleeding surface

The method has proved ideally simple and easy to use, and it has been proved that it is an excellent means of inspecting the uterine cavity The technique is of particular value for two gynæcological problems encountered at Radiumhemmet, for the solution of which there were hitherto no reliable methods These are the exact localization and extension of carcinomatous growths since these two factors are decisive in the choice of treatment, either surgical, radiological or combined surgical radiological

In all cases examined, a good view of the uterine cavity was obtained when the instrument was held on a level with the internal uterine mouth Any area of particular interest could be more closely studied by moving the instrument nearer to the uterine wall A biopsy of tissue from a suspect area, revealed by hysteroscopy can be made prior to curettage

In recent years, experience has shown that most cases of cancer of the uterine corpus are more or less highly differentiated adeno carcinomas These tumours have a tendency to spread exo phytically in the uterine cavity, whereas the low differentiated, often solid carcinomas seem to have a more marked tendency towards rapid infiltration of the muscular wall of the uterus (Kottmeier, 1962) From a therapeutic point of view, it is therefore of importance to distinguish between these and the differentiated adenocarcinomas (Kottmeier 1959 Gusberg, Jones and Towell, 1960) Sometimes it is difficult for the pathologist to determine the degree of differentiation by ex amining the material obtained by curettage The observation that the highly differentiated tumours in the corpus are seen through the hysteroscope as papillomatous sometime cauliflower like ex crescences, whereas the poorly diffentiated have the appearance

of a flat silvery mat in the uterine wall, is of interest and might contribute to the differential diagnosis

With the method described it is possible to obtain a good view of the uterine cavity The method has proved quite satisfactory in clinical use From a scientific point of view, it would have been of interest to document the hysteroscopic observations with photographs Up to now, it has not been feasible to take photographs in a living human being because of the long exposure time (more than 50 seconds) The calibre of the instrument is too small to hold flashlight equipment Photographic experts have been entrusted with the task of solving this problem, and the work is already in hand

It is possible that previous hysteroscopic methods could reveal changes in the uterine canal The question is, however, whether these methods permitted localization and determination of the extension of the tumour and its relation to the cervix and the internal cervical os

By the method used in the present investigation, it has been possible, without undue trauma, to determine the exact position, appearance and margins of a tumour

SUMMARY

A report on the clinical application of a new hysteroscopic method in 40 patients with cancer of the uterine endometrium has been presented The instrument employed consists of an endoscope with a thin rubber balloon slipped over the objective The completely transparent rubber balloon, when distended, fills out the uterine cavity and keeps it dilated so that it is accessible for inspection At the same time, bleeding is prevented In all cases examined, the results of the inspection were entirely satisfactory, and the exact position and extension of tumours could be determined No complications occurred

A review of the literature in this field is given

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HYSTEROSCOPY THROUGH A TRANSPARENT RUBBER BALLOON IN PATIENTS WITH UTERINE BLEEDING

BY

TORSTEN SILANDER

Hysteroscopy is an old procedure which was first introduced by Pantaleoni in 1869 He used an open tube with an external light source Since then, many investigators have reported improvements in the method (David, 1908, Heineberg, 1914, Rubin, 1925, Seymour, 1926, Mikulicz-Radecki and Freund, 1927, Gauss, 1928, Segond, 1934, 1935, 1936, 1937, Schröder, 1934, Schack, 1936, Norment, 1943, 1948, 1949, 1952, 1956 a, b, c, 1957,) Finally these investigations led to the use of a water rinsing system, by means of which obscuring blood could be washed away Using a McCarthy panendoscope with water rinsing system, Englund, Ingelman-Sundberg and Westin (1957) obtained satisfactory results In only 2 5 per cent of the 165 cases examined did obscuring bleeding occur In 1957 Norment reported attempts at hysteroscopy by means of an instrument with a transparent rubber tissue bag over the objective He eventually abandoned his method because the large sized rubber bag wrinkled when introduced into the uterus and rendered inspection impossible

In 1962 Silander described an experimentally developed method for hysteroscopy In the instrument used a thin completely transparent latex-rubber balloon was slipped over the objective The rubber balloon could be distended by injection of liquid

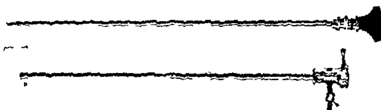


Fig 1 The Silander Wolf hysteroscope in its three component parts a tele scope (a) a thin transparent rubber balloon (c) and an outer tube (b)

through a thin catheter attached along the telescope In this way the uterine walls were kept apart and bleeding was prevented

The object of the present investigation was to ascertain whether the method would be clinically applicable in general gynæcology

Method

The method used is a development of the technique for hys teroscopy described by Silander (1962), which was based on model experiments on uterine preparations This technique had been worked out after a method for inspection of blood filled cavities described by Carlens and Silander (1961) It seemed to fulfil the basic requirements for endoscopy of the uterine cavity, *i e* capacity to keep the cavity distended and minimal stimulation of the easily traumatized endometrium

Instrument

The instrument employed consists of an outer tube of thin stainless steel 7 mm in diameter, containing a telescope, 5 mm in diameter with a fore-oblique objective A leak proof union is en sured between the telescope and the outer tube A cock with

The instrument has been manufactured by AB Stille-Werner Stockholm Sweden and Richard Wolf Knittlingen Germany

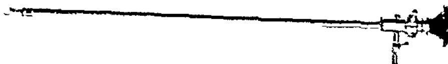


Fig 2 The outer tube is placed over the telescope and locked into position with a water-tight closure The rubber balloon is rolled on the distal part of the outer tube and locked in position by a metal ring





Fig 3 Detail of the expanded balloon

fitting for Lurer-Lok syringes is provided at the proximal end of the outer tube

The instrument is shown in Figs 1–3 It is made up of three parts

a) a telescope
b) an outer tube
c) a transparent rubber ballon

The telescope (a) is 5 mm in diameter and has a fore oblique objective (160°) An electric bulb is placed in front of the objective The connection between the telescope and the outer tube (b) provides a water-tight seal A cock with fitting for Luer Lok syringes is located near the occular Liquid injected through the cock is conveyed through the space between the telescope and the

outer tube to the distal end of the latter A rubber balloon (c) is slipped over the lamp, the objective and the conical distal end of the outer tube, where it is secured in position by means of a metal ring The thin rubber balloon which is 5 mm in diameter, is completely transparent even if it is only slightly distended

When the instrument is assembled, the desired amount of liquid can be injected into the rubber balloon by means of the syringe connected to the cock near the occular

The outer tube and the syringe are sterilized by boiling The rubber balloon and the telescope are sterilized with ethylene oxide

Procedure

The patient is placed in the lithotomy position and prepared as for a curettage A speculum is introduced and the cervix grasped with a volsellum outside the cervical canal in order not to damage the latex balloon After measurement of the depth of the uterus, the cervix is dilated to Hegar 7 or 8 Then the hysteroscope with the collapsed balloon is introduced, the lamp is lighted, an adequate amount of liquid is injected into the balloon by means of the syringe and the examination is commenced Generally, from 6 to 12 ml saline solution is sufficient to fill out the cavity completely and to keep the uterine walls separated In cases in which the uterine cavity is very large, up to 16 ml may be required

In most cases, the examination is started with inspection of the internal uterine os which is easily accessible for examination With the objective on a level with the internal os, slight pressure on the syringe is sufficient to keep the cavity completely distended so that the entire uterine cavity as well as the two tubal orifices are visible at the same time For closer inspection of interesting areas, the instrument is moved nearer to the uterine wall The instrument can be easily moved in all directions inside the rubber balloon The degree of dilatation of the uterus can be varied as required by varying the pressure exerted on the syringe In order to achieve the best possible result, the cock of the syringe should not be closed during the examination The balloon follows exactly the contour of the uterine wall, and even soft growths which could be expected to be compressed by the pressure applied, can be closely observed



Fig 2 The outer tube is placed over the telescope and locked into position with a water-tight closure The rubber balloon is rolled on the distal part of the outer tube and locked in position by a metal ring





Fig 3 Detail of the expanded balloon

fitting for Lurer-Lok syringes is provided at the proximal end of the outer tube

The instrument is shown in Figs 1–3 It is made up of three parts

a) a telescope

b) an outer tube

c) a transparent rubber ballon

The telescope (a) is 5 mm in diameter and has a fore oblique objective (160°) An electric bulb is placed in front of the objective The connection between the telescope and the outer tube (b) provides a water-tight seal A cock with fitting for Luer Lok syringes is located near the occular Liquid injected through the cock is conveyed through the space between the telescope and the

Hysteroscopy + endometrial curettage The length of the uterine cavity was 8 cm. The cervix was dilated to Hegar 8 The endoscope was introduced and the balloon inflated with from 8 to 12 ml saline solution. Except for an inward curvature near the left cornu the uterine walls were even and smooth The following curettage yielded a moderate result It was noticed that the curette jumped over an inward bend to the left in the posterior wall Hysteroscopy was repeated and again presented a clear view of the cavity The right tubal orifice was normal but the left one was compressed towards the mid line by a whitish structure of the size of a finger tip in the left wall The growth was considered to be a submucosal fibroid

When examined histologically, the material obtained from the curettage was found to consist of atrophic sclerotic pieces of endometrium.

There were no postoperative complications or rise in temperature The highest postoperative temperature recorded was 37 3 C Hystero-salpingography performed 6 days after the curettage revealed a rather large uterus There was a rounded indentation 1 5 by 2 cm deep probably caused by fibroids in the left uterine wall The tubes were not inflated with contrast medium

Case 2 (751/62)

A 50-year-old woman had 4 normal deliveries Curettage had been performed in 1960 because of irregular uterine bleeding She was readmitted in May 962 because of heavy irregular menstrual periods Gynæcological examination revealed a slightly enlarged somewhat irregular fibroid uterus No adnexal pathology was palpable

Hysteroscopy + endometrial curettage Length of uterine cavity 10 cm. Cervix was dilated to Hegar 8 The endoscope was introduced and the balloon inflated with saline solution Inspection of the cervix revealed no changes The cavity was found to be somewhat enlarged A rather pale structure of the size of a walnut was observed in the front wall near the left tubal orifice Otherwise there were no pathological findings The abnormal area observed on hysteroscopy was then scraped out with a sharp curette Abundant polypoid material was obtained and the wall felt slightly uneven In the other parts of the cavity the walls felt smooth and firm. On repeat hysteroscopy the abnormal area was seen to have a relatively smooth glistening white surface No changes were observed in the other parts of the cavity A clear view of the entire cavity was obtained

Histological findings Mainly normal proliferative phase endometrium with many polypoid areas

Postoperative condition No complications No rise in temperature above 37 2 C

Case 3 (1733/61)

The patient was 48 years old and had had 4 normal confinements. Menstrual periods had been regular with a cycle of 4 days/28 days but the

Table I *Summary of Cases*

Age in Years	Parity			Bleeding		Previous Curettage	Haemoglobin <11 g	Sed Rate >15 mm hour	Length of Uterine Cavity	
	Nulli	Primi	Multi	Cyclic	Acyclic				>9 cm	9 cm or more
Up to 35	1			1			1	1		1
36—50	2	4	6	2	10	8	4	4	5	7
51 or more	1	1			2	2			1	1
Total	4	5	6	3	12	10	5	5	6	9

By varying the pressure in the balloon, it is possible to study folds in the mucous membrane and small polyps The plicæ palmatæ in the cervix are easily distinguishable, but can also be smoothed out by increasing the pressure in the balloon

Material

Fifteen women whose age varied between 31 and 53 years (mean age 44 8 years) have been examined by the method described during the years 1961 and 1962 The examinations were carried out in the Clinic for Gynæcology of Sabbatsbergs sjukhus, Stockholm Three of these patients had regular and 12 irregular bleeding Ten patients had undergone earlier curettage In 2 patients the uterus was retroverted, in the others upright or anteverted In conjunction with the hysteroscopy, curettage was performed in all patients The material obtained from the curettage was examined histologically Hysterosalpingography was performed in 4 patients Subsequent hysterectomy was performed in two patients

The material (Table I) comprised patients with submucosal fibroids, corpus polyps, endometrial hyperplasia and cases with normal mucous membrane A representative case from each one of these groups will be described here

Case 1 (1646/61)

The patient, 51 years old, had had one normal confinement Curettage was performed in 1953 because of irregular uterine hæmorrhage She was readmitted in October 1961 for the same reason The gynæcological examination revealed an anteflexed, firm, mobile uterus of normal size

Course and Results

Hysteroscopy was performed by different investigators Most of them had never used the method before Since the examination was performed in conjunction with curettage, anæsthesia was given in all cases In one case, the balloon slipped off the instrument The balloon was removed with forceps, and then the examination proceeded without complications Otherwise the examinations were easily performed, the uterine cavity was clearly visible, and bleeding did not obscure the view in any of the cases examined Hysteroscopy was performed both before and after curettage with the same good result The bleeding resulting from the curettage offered no obstacle to the examination Submucosal fibroids were rather more easily distinguishable after than before curettage The patients with retroverted uteri presented no difficulties

The observations made during hysteroscopy and the result of the histological examination corresponded exactly except in two cases In both these cases, the hysteroscopic inspection indicated the presence of a submucosal fibroid, whereas the histological examination only revealed normal mucous membrane However, by hystero salpingography, filling defects were discovered in the abnormal area observed at hysteroscopy In the two other cases in which hystero salpingography was performed, there were no filling

Table II Comparison between Hysteroscopic and Histological Findings

	Hysteroscopic Findings				Histological Findings			
Age in Years	Normal	Submuc Fibroid	Polyp	Hyperplasia	Normal	Fibroid	Polyp	Hyperplasia
Up to 35		1				1		
36 — 50	8	2	1	1	9	1	1	1
51 or more		2			1	1		
Total	8	5*	1	1	10	3*	1	1

In two cases the submucosal fibroid observed in the hysteroscope was not confirmed by the histological findings In both these cases hystero-salpingography revealed a filling defect in the abnormal area visualised at hysteroscopy

penultimate menstruation had lasted 14 days When the patient was admitted to the hospital, bleeding had been continuous for 12 days it had been copious and the patient was very weak and tired and had fainted on two occasions Gynæcological examination revealed that the uterus was of the size of a fist, myomatous, anteflexed, firm and mobile No adnexal pathological changes were palpated

Hysteroscopy + endometrial curettage Length of uterine cavity 9 cm Cervical dilatation to Hegar 9 The endoscope was introduced and the balloon filled with saline solution A clear picture of the uterine cavity was obtained The examination revealed a pronounced hyperplastic endometrium with folds projecting about 0 5 m into the cavity No isolated polyps were discovered, but the entire endometrium had a polypoid appearance Curettage was performed and yielded rich polypoid material, particularly from the posterior wall Except for a slight indentation in the left posterior wall, the cavity felt smooth When introduced again, the hysteroscope revealed residues of mucous membrane Otherwise the walls were smooth and even. To the left in the posterior wall, a slight smooth inward curvature was noticed There were no signs of submucosal fibroids

Histological findings Large hyperplastic endometrial areas with irregular, often cystically dilated glands in the proliferative phase with a markedly stained epithelium Abundant stroma rich in cells No true polyps. Diagnosis Metropathia hæmorrhagica cystica

On the fourth postoperative day, the patient s temperature was 37 8 C. Thereafter there was no rise in temperature above 37 4°C

Case 4 (1658/61)

The patient was 46 years old and had had one normal childbirth in 1940 Menstruation had always been regular but heavy, with a cycle of 7 days/30 days For the last 4 years, the patient had suffered from anæmia and had been very tired She was admitted to the hospital because of a suspected submucosal fibroid On gynæcological examination, the uterus was found to be anteflexed, of normal size, firm and smooth

Hysteroscopy + endometrial curettage Length of uterine cavity 9 cm Cervix dilated to Hegar 9 The endoscope was introduced and the balloon filled with saline solution A clear view of the uterine cavity was obtained The walls appeared to be smooth and evenly covered with normal mucous membrane Accumulation of blood in the tubal orifices impeded examination of these organs The material obtained from the subsequent curettage seemed to consist of normal mucous membrane Hysteroscopy was repeated and it was now possible to inspect the tubal orifices No pathological condition could be discovered

Histological findings Normal endometrium in the proliferative phase

Postoperative condition No complications occurred The highest temperature was 37 2°C

and rœntgenological examinations In the two cases in which the histological and hysteroscopic findings differed the correctness of the hysteroscopic observations was supported by the following hystero-salpingography, which revealed a filling defect in the area in which hysteroscopy had indicated submucosal fibroids Considering the fact that fibrous tissue is generally not evacuated in ordinary curettage when only normal pressure is exerted on the curettage, there is reason to believe that no representative tissue was obtained from the curettage in question, and that the hysteroscopic observation was correct Thus the hysteroscopic diagnosis was correct in all cases examined

The method described is simple and easy to use and provides an excellent means of inspecting the uterine cavity This is also evidenced by the fact that the majority of the hysteroscopic examinations were carried out by investigators, who had never used this method before

SUMMARY

The Silander hysteroscope has been used in 15 patients with uterine bleeding The method and instrument are described, and an account of the patients examined is given A good view of the uterine cavity was obtained in all cases studied No complications occurred The hysteroscopic diagnosis was correct in all cases in spite of the fact that the examinations were performed by different investigators

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defects, and both the hysteroscopic and the histologic examination showed the same picture of normal mucous mebrane

Hysterectomy was performed in two cases In one of these a submucosal fibroid had been diagnosed both by hysteroscopic and histologic examination In the other case, both these examinations had shown a normal mucous mebrane In both cases, the diagnosis was verified by examination of preparations after the operation The hysteroscopic and histological findings are accounted for in Table II

No salpingitis or any other postoperative complication occurred One patient, who had been given a blood transfusion, had a temporary rise in postoperative temperature to 38 8°C (rectal temperature) In no other case, the body temperature exceeded 37 8°C In all cases examined, the mean maximum postoperative temperature was 37 4°C

Discussion

The purpose of the present investigation was not to analyze the clinical material, but to ascertain whether the hysteroscopic method described would be clinically applicable

Rubin (1925, 1956) observed that endoscopic examination of the uterine cavity was impeded by two characteristic features of the uterus, *i e* the slit shaped cavity with the uterine walls practically in close apposition, and the readiness with which the endometrium bleeds on contact with any instrument Schack (1936) shared this opinion and remarked that if the uterine cavity could really be dilated like the urinary bladder in cystoscopy, the problem of hysteroscopy would be solved In the 50 cases examined by Schack, a satisfactory view of the uterine cavity was obtained only in 21 cases In all the other cases, the view was obscured by bleeding

These difficulties seem to have been overcome by the present method using an inflatable transparent rubber balloon In all cases examined by this method, a satisfactory result of the examination was obtained The view of the cavity was never obscured by bleeding, either before or after curettage The hysteroscopic findings were in close agreement with the results of the histological

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EXCRETION OF ŒSTROGENS 17-KETOSTEROIDS AND 17 OH CORTICOSTEROIDS IN IRRADIATED CERVICAL CARCINOMA

BY

ARNE LINDELL AND M. O RAUD

Introduction

One of the first to demonstrate that œstrogens might have some connection with cancer was Lacassagne in 1932 who succeeded in inducing breast cancer in male mice by a longterm administration of œstrogens Investigations along the same lines have since been made by several authors among them Overholser and Allen (1936) Engle and Smith (1935) Gardner *et al* (1939), and Nelson (1939) Using mice guinea pigs and even monkeys they were able to induce precancerous or cancerous changes in the cervix uteri However, in most of the experiments the doses used far exceeded physiological levels Moreover in certain strains of experimental animals the innate cancer frequency was high Great caution must therefore be exercised in drawing conclusions about the carcinogenic effects of œstrogens from these investigations

It is well known that œstrogens have a stimulating effect on the female genital organs and breasts Long term administration of large doses of œstrogens can give rise to epithelial metaplasia of the genital organs not only in animals but also in *man* In pregnancy œstrogen values are physiologically high We know

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Most of the investigations previously published are based on biological or earlier chemical procedures In 1955, Brown published his method of fractionated œstrogen determination, but concerning uterine cancer no large investigations based on this method have yet been reported We therefore decided to use it in a study of the fractionated œstrogen excretion in cases of cervical carcinomas Excretion of 17 ketosteroids and 17 OH corticosteroids in urine was also investigated The aspects that were studied are as follows

1 The level of excretion before therapy
2 Changes in excretion during and after radiotherapy
3 The correlation between excretion and prognosis

Materials and Methods

The material comprises 17 cases of squamous cell carcinoma of the cervix in fertile women between 23 and 48 years of age, the mean age being 39 4 years The cases were classified according to the international classification and have the following distribution

Stage I - 6 cases
Stage II - 9 cases
Stage III - 2 cases

All cases received conventional radiotherapy in accordance with the procedure of the Radiumhemmet, Stockholm This consists of radium applications both intrauterine and vaginal, on two occasions at an interval of three weeks The patients received a vaginal dose of about 4000 mgh and an intrauterine dose of 3000 to 4000 mgh After another three weeks, rœntgen treatment was started The usual four fields round the pelvis were irradiated each with 5×400 r The total radiation dose to which the ovaries were exposed was between 3000 and 4000 r Urine samples for hormone titration were taken during the course of radiotherapy, the first immediately before the beginning of treatment (in order to determine the level of excretion in non irradiated women) the second when the patient returned for her second radium application the third when rœntgen therapy was started and

that cancer of the cervix occurs more frequently in multiparae than in nulliparae One explanation suggested for this is that the epithelium of the cervix undergoes great proliferative and meta plastic changes as a result of the high œstrogen levels during pregnancy Cases of cancer of the uterus have been reported in connection with abnormally high endogenous œstrogen production or after a long period of therapeutic œstrogen administration In this context it may be mentioned that Bainborough (1951) found a significant correlation between endometrial hyperplasia and cervical cancer, while Bayly and Green (1952) came to the opposite conclusion

That œstrogens provoke cancer in man has never yet been proved However, even if they have no direct cancerogenous effect it is likely that they stimulate the growth of cancer cells in the same manner as the growth of normal cells It has also been suggested that carcinogenic substances may arise in the steroid metabolism of the body The question of œstrogen content and œstrogen excretion in cancer of the uterus has therefore aroused considerable interest

Many different methods, biological as well as chemical, have been used for determining œstrogens in urine It should be noted that the biological methods have usually given higher values than the chemical In 1930 Laqueur and coworkers published an investigation of œstrogen excretion in cases of uterine cancer They demonstrated a moderate to considerable increase in biological œstrogen activity This was supported by many other investigators, among them Grattarola (1949), Balassi and Ricca (1951), Izabolinskaja and Tschebotarew (1953), Liu (1955), and Nakajima (1957) On the other hand, there are many investigations where normal or low œstrogen values have been found in connection with cancer of the uterus Siebke (1931), Assman (1931), Aichel (1932), Bret (1955), Buntner and Dux (1955), and Murata (1961) may be mentioned in this connection Some of these authors found changes in the œstriol/œstrone+œstradiol quotient in cases of cancer of the uterus In most cases the œstriol excretion had decreased This suggests a possible disturbance of œstrogen metabolism in this disease

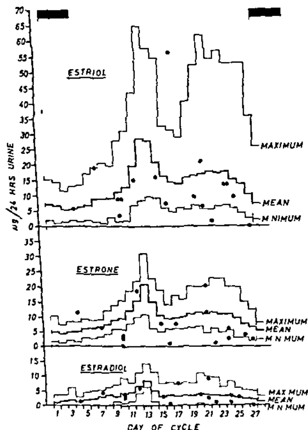


Fig 1 Œstrogen excretion before irradiation Values plotted on a diagram of values obtained from normal women (Diagram from Brown and Matthew 1962)

within rather wide limits but the majority lie below the mean curve The œstriol/œstrone + œstradiol quotient in the present series is 1 2 i e higher than the normal value of 1 0

The 17 keto- and 17 OH corticosteroids do not fluctuate over the menstrual cycle but as is well known the 17 ketosteroid excretion depends on age Fig 2 shows the 17 ketosteroid values in relation to the patients age and it is seen that the values are usually within normal limits The excretion of 17 OH corti-

the fourth and last after a varying period, depending on the individual circumstances The interval before this final titration varied between 18 and 43 weeks, the mean being 33 weeks after the beginning of irradiation The œstrogen determinations were made on 48 hour samples of urines, according to Brown's modified method (1955, 1957), comprising fractionation into œstrone, œstradiol and œstriol The determinations of 17 ketosteroids and 17-OH corticosteroids were carried out on the same urine, the former according to Zimmermann modified, the latter according to Norymberski

In all cases the observation period has been more than two years During this time five of the patients have died of cancer while the remaining twelve cases are free of symptoms

Results

1 *Level of excretion before therapy*

An attempt was first made to determine in what way, if any, the level of excretion before therapy differs from that in normal patients Concerning the excretion of œstrogens, the question cannot be answered without a knowledge of the menstrual phase at the time of collection of the urine For all three œstrogen fractions investigated excretion varies considerably during the menstrual cycle It would have been desirable to make the titrations with all the patients at exactly the same point in the cycle This, however, was impossible for practical reasons, as therapy cannot be postponed until a suitable phase in the cycle is reached

The phase determination in our material is based on the statements of the patients about their last period on endometrial biopsies and, in a few cases, on cytological examination of vaginal smears By means of the information collected in this way it was possible to estimate the day of the cycle fairly accurately The titration values obtained are shown in Fig 1 It can be seen that they are distributed over the whole menstrual cycle The normal values are taken from Brown (1962) They correlate closely with those obtained in our own hormone laboratory The values for the excretion of the various œstrogen fractions are distributed

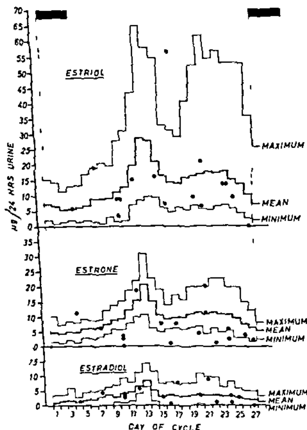


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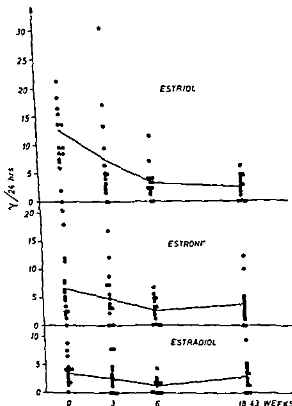


Fig 3 Excretion of œstrogens before during and after irradiation

months post irradiation œstriol excretion remained at the same low level The excretion of œstrone and œstradiol increased somewhat especially the latter where the increase was statistically significant (0 05>p>0 01 t test) The œstriol/œstrone+œstradiol quotient differed for different patients but the median showed a distinct decrease to 0 5 from the original value of 1 2 (Table I)

The excretion of 17 ketosteroids rose slightly during the first weeks following irradiation but the increase was not statistically significant The 17 OHCS excretion remained unchanged during the whole period of observation See Fig 4

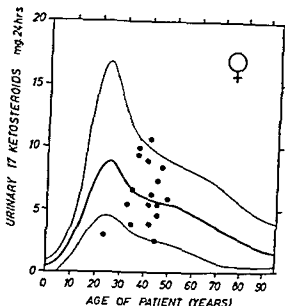


Fig 2 Excretion of 17 keto-steroids before irradiation Values plotted on a diagram of values obtained from normal women (Diagram from Hamburger 1948)

costeroids is shown in Fig 4 The values lie within normal limits There is thus no tendency to exceptionally high or low values in the present study

2 *Changes in excretion during and after radiotherapy*

As is well known irradiation induces an atrophy of the ovaries and a decrease in the production of œstrogens It is of interest to see how rapidly these changes take place and how the different œstrogen fractions are affected Another problem is to see if this radiological castration is as effective and as rapid as oophorectomy As is shown in Table 1 and Fig 3 there was a decrease in all three œstrogen fractions, which was most pronounced with œstriol Within six weeks this process was more or less complete, having reached postmenopausal values In all three fractions the decrease was statistically significant, *i e* in œstriol $0.01 > p > 0.001$ (t-test) and in œstrone and œstradiol $0.05 > p > 0.01$ (t test) Concerning the œstrogen values taken at least four

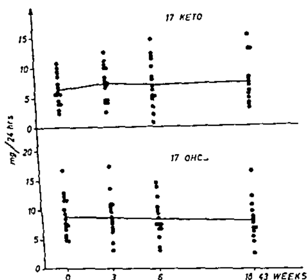


Fig 4 Excretion of 17 keto-steroids and 17-OH-corticosteroids before during and after irradiation

fluence of œstrogen production on tumour formation can be established studies of the œstrogen pattern and its variation may be of prognostic significance

If œstrogen production is increased it should be revealed in increased excretion It is only lately with the arrival of the recent chemical methods for fractionated œstrogen titration that it has been possible to obtain reliable results Only a few investigations have so far been published especially concerning uterine cancer and the results are somewhat contradictory In our material on cervical carcinoma we have been unable to note any increased œstrogen production On the contrary the excretion is somewhat below normal, and this applies to all three œstrogen fractions

According to Diczfalusy and Lauritzen (1961), the values in mammary cancer are on the whole the same as in healthy women It therefore seems as if no increase in the œstrogen excretion occurs in either cancer of the breast or cancer of the uterus

Table I

	Urinary Excretion in 24 Hours			
	Before Irradiation	3 Weeks Later	6 Weeks Later	18–43 Weeks Later
Œstrone	6 6±1 4	4 8±1 2	2 6±0 6	3 7±0 9
Œstradiol	3 5±0 5	2 6±0 6	1 2±0 3	3 0±0 6
Œstriol	12 7±3 0	7 4±2 0	3 4±0 8	2 6±0 5
Quotient Œstriol / Œstrone + œstradiol	1 2	0 8	0 9	0 5
17 keto-steroids	6 4±0 6	7 3±0 7	7 1±1 0	7 0±1 1
17 OH corticosteroids	8 8±0 8	8 8±0 8	8 5±0 9	8 2±1 0

Results given as arithmetic mean ± standard error of mean except the quotient which is given as median value

3 *Correlation between excretion and prognosis*

No certain correlation could be found between the prognosis and the excretion of the various œstrogen fractions and 17 keto and 17-OHCS Of the 17 cases five died, all within 1 ½ years Of these five, three were at Stage II and two at Stage III All six cases at Stage I are alive, as well as six cases at Stage II There are therefore 12 patients alive and symptom free after an observation period of over two years

Discussion

Normally, œstrogens have a stimulating effect on certain female organs, especially the uterus and breasts It is therefore reasonable to postulate some connection between œstrogens and tumours in these organs There are several ways in which œstrogens and tumours might be related Women with cancer of the breast or of the uterus may have an increased œstrogen production or a changed œstrogen metabolism It may also be that normal œstrogen production aggravates the cancer and that a decrease in production would have a favourable effect If an in-

as after oophorectomy, had been reached. In the study of Persson and Risholm all three œstrogen fractions retained the same level for 8–10 days after oophorectomy and then declined to reach postmenopausal levels after six weeks The reasons for this retention for the first few days after the operation are not fully understood Possibly it is due to postoperative stress causing an increased adrenal œstrogen excretion However the decrease to postmenopausal levels takes about the same time in the oophorectomized patients as in our irradiated ones

Concerning the late values—at least four months after radiotherapy—our material shows that œstriol excretion remained at the postmenopausal level, while a slight increase is noted for œstrone and œstradiol, statistically significant in the case of the latter The resemblance between this picture and that in the oophorectomized patients of Persson and Risholm is striking There too, there was a gradual increase in œstrogen excretion, especially of œstradiol It should be mentioned that Persson and Risholm s patients had been given cortisone from the 11th day post oophorectomy This depresses the œstriol component mainly The late increase seems to indicate an extraovarian origin of the secretion

From the above the advantages of oophorectomy over radiological castration appear questionable as a means of depressing œstrogen production On the other hand the possibility that the ovaries may retain a certain hormone production capacity in some cases cannot be excluded

As previously stated by other authors the *œstriol/œstrone+œstradiol* quotient which is normally about 1 0 in fertile women drops to 0 2–0 3 after castration This means that the œstriol decrease is greatest In our series the values varied in different individuals but median values indicate a decline from 1 2 to 0 5 (Table I) The values are thus somewhat higher than in a normal series of non cancerous women Although these results are not conclusive a change in the œstrogen metabolism may be suspected In this connection it should be noted that in healthy patients the quotient is 1 0 even after the menopause

Several authors among them Puck and Hübner (1956) and Borglin (1959) have pointed out that œstriol normally affects

Even if women with cancer of the breasts or uterus have no increased œstrogen excretion it is possible that there may be a change in œstrogen metabolism Several authors have investigated the œstriol/œstrone+œstradiol quotient and found an increased value in cases of uterine cancer In our series also, the quotient is increased This may indicate an altered œstrogen metabolism It is not impossible that the different œstrogens have quite different characteristics from the point of view of cancer stimulation

There is no doubt that mammary cancer is affected by normal œstrogen production It is well known (*cf* Diczfalusy and Lauritzen, 1961) that œstrogen administration aggravates the condition, while a decrease in œstrogen production leads to remission This decrease can be induced by oophorectomy Attempts have been made to eliminate the remaining œstrogen production by means of adrenalectomy or hypophysectomy

It is possible that cervical cancer reacts in the same way as mammary cancer, *i e* the prognosis improves if œstrogen production is kept low Oophorectomy has been tried in such cases However, the results have not been encouraging In fact, in many cases the tumour has progressed more rapidly, probably owing to the trauma induced by the operation itself

The radiotherapy conventionally used in cervical cancer causes radiological castration The question is whether this puts an end to ovarian function as effectively as oophorectomy, or whether some function remains In order to clarify this point we have compared our own radiologically castrated series with that of Persson and Risholm (*cf* Diczfalusy and Lauritzen 1961, p 431) in which oophorectomy had been performed in 16 fertile women with mammary cancer The reason for choosing this particular study for comparison was that the hormone titrations had been carried out at the same laboratory and in the same manner

In our series there is a decrease in all three œstrogen fractions most pronounced in the œstriol This fully agrees with the results usually obtained in rœntgen castration in connection with mammary cancer In our study the decrease was usually completed within six weeks At that time postmenopausal values the same

was within normal limits and remained constant during and after irradiation therapy

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mainly the cervix and the vagina Possibly a high œstrioltitre may stimulate cervical cancer In our investigation the quotient is raised, indicating an increased œstriol secretion The series is too small for any firm conclusions, but the possibility that a disturbance in the œstrogen metabolism may stimulate the formation and development of cancer is not excluded

Concerning the correlation between œstrogen excretion and prognosis, it is impossible to draw any definite conclusions from our investigation The œstrogen production in the five patients who died showed wide individual variations but the mean values did not diverge significantly from the rest of the series

SUMMARY

Fractionated œstrogen determinations according to Brown (œstrone, œstradiol and œstriol) were made in 17 cases of squamous cell carcinoma of the cervix uteri in fertile women The determinations were carried out before, during and after radiotherapy

The opinion that œstrogen production is exceptionally high in women with cervical cancer could not be confirmed On the contrary, for all three œstrogen fractions the values were throughout slightly below normal in our study

After irradiation of the ovaries with a dose of 3000 to 4000 r the œstrogen excretion declined rapidly The decrease was complete within six weeks, reaching postmenopausal values The decrease occurred at about the same rate as after oophorectomy The decrease for œstriol was permanent The œstrone and especially the œstradiol production, however, increased again, according to titrations carried out more than four months later

The pretherapy œstriol/œstrone+œstradiol quotient of 1 2 dropped to 0 5

Of the 17 cases investigated, five died within 18 months, all of cervical cancer Two years post irradiation the remaining 12 cases are still asymptomatic No significant abnormal œstrogen excretion could be noted in the cases who died

The excretion of 17-ketosteroids and 17-OH corticosteroids

was within normal limits and remained constant during and after irradiation therapy

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SARCOMA OF THE VAGINA

Report of a Case

BY

ANNI HELO

Sarcoma of the vagina is a very rare tumour In 1935 Mc Farland (1958) noted 58 cases of it in the Anglo-Saxon literature Tracy (1930) described four cases Diehl and Haught (1946) reported one case of vaginal sarcoma in 4,000 gynæcological patients Woodruff and Brack (1958) found four cases of fibrosarcoma of the vulvo urethral region during the period 1934–53

The incidence of sarcoma of the vagina in children is four times as great as in adults Here, it is usually a mixed mesodermal tumour, generally botryoid in type In adults, the sarcoma is a mixed mesodermal tumour either or a sarcoma of common type The most usual is a fibrosarcoma of fibroblastic origin, generally rich in reticulin and collagen, though there are also forms in which these elements are not prevalent The histological picture shows long fusiform cells with longish hyperchromatic nuclei and an abundance of mitoses The next most common are lipo-, rhabdomyo- and leiomyosarcomas The last mentioned is said to originate in the rectum, the uterus, the bladder or the retroperitoneal area According to Schram (1958), it has its origin in the muscular tissue of the rectum or the vascular walls, or in embryonal cells (Novak, E, Novak, E R, 1958)

Clark and Martin (1958) suggest a traumatic ætiology, but this is difficult to confirm

The commonest symptom of this sarcoma is inflammation of





Fig 1 Sarcoma of the vagina

the affected side At a later stage this is followed by pain with general symptoms of loss of weight weakeness and fever After removal the tumours usually recur locally before metastasizing the latter generally takes place by the hæmatogenous route In the final stage however metastases may appear in the lungs, kidneys liver and omentum

The treatment of vaginal sarcoma is extensive local excision, X ray treatment is rarely effective

Since this tumour is rare the following account of a case of

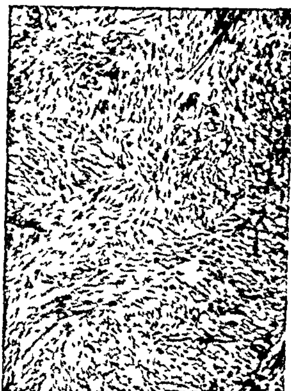


Fig 2 Histologic section of the tumour (van Gieson Approx × 150)

vaginal sarcoma treated surgically at the Department of Obstetrics and Gynæcology I, University Central Hospital, Helsinki, may be of interest

The patient was a 50 year old woman from Helsinki the wife of an electrical fitter Menstruation had been regular terminating 16 years previously Para I 1935 1944 operation for goitre 1955 operation for gall stones The patient s mother had died of uterine cancer

The patient was admitted to the Women s Clinic in 1956 The diagnosis was leiomyoma of the vagina Immediately behind the hymenal ring there was an easily accessible tumour the size of a plum firm and somewhat uneven of surface The tumour was extirpated and subsequent microscopical examination showed leiomyomatous tissue throughout richly cellular Comparatively little connective tissue was found in the tumour, the bulk of which consisted of smooth muscular tissue light nuclear polymorphism was observed The growth was considered probably benign, judging from its structure and absence of mitoses Because of the abundance of cells and the sight polymorphism the case remained under observation (v Numers)

In April 1959 the patient reported a recurrence of the tumour, she felt in

creasing discomfort in the lower abdomen but there was no discharge She was admitted to the hospital in February 1960 Between the vagina and the rectum on the right side a slightly protruding and not freely movable tumour was found adherent to the mucous membrane of the rectum It was the size of a large plum firm and insensitive On its cranial side there was a firm mobile nodule the size of a pea The external os of the uterus was clean the corpus of the uterus small atrophic in retroversioflexion position and nothing of abnormal appearance was found laterally (Fig 1)

The tumour was removed together with the part of the mucous membrane of the vagina attached to it The tumour was clearly defined though it was firmly attached to the rectum for a length of about two centimetres

The cut surface of the tumour was reddish very soft and caseous The pathologico-anatomic specimen revealed dense intertwining clusters formed of fusiform cells The nuclei proved to be polymorphic some being rather large However there were no signs of hyperchromasia and relatively few mitoses The diagnosis was leiomyosarcoma (v Numers) (Fig 2)

The patient s general state of health was good Sedimentation rate was 7 mm hæmoglobin 71/11 4 Wasserman test was negative and urinanalysis showed nothing abnormal The patient made a good recovery

SUMMARY

A case is reported of a rarely occurring vaginal sarcoma in a woman aged 59 The patient was admitted to the Womens Clinic in Helsinki in 1956 Behind the hymenal ring there was a tumour the size of a plum which was extirpated The pathologico-anatomic diagnosis was leiomyoma In 1959 the patient had a recurrence of the tumour It was now a clear case of leiomyosarcoma The tumour was extirpated and the patient made a good recovery

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URETHRAL CLOSURE IN THE FEMALE AND ITS INSUFFICIENCY IN STRESS INCONTINENCE EXPERIENCES WITH A BLADDER-URETHRA MODEL

BY

GÖRAN ENHÖRNING AND BJÖRN WESTIN

Numerous methods of surgical treatment for stress incontinence have been developed over many years but no method is satisfactory under all conditions, partly due to incomplete understanding of the urethral closure mechanism Experience has shown certain types of operation to be of value, but it has not always been easy to evaluate the improvement likely to result from a specific type of surgical procedure Certain anatomical changes have been described, however, which are found in most cases of stress incontinence and seem to offer a basis for objective pre operative evaluation The cysto-urethrogram often shows funnelling of the upper urethra (Barnes, 1940 Hodgkinson, 1953, Ingelman-Sundberg, 1949 Jeffcoate and Roberts 1952, Muellner, 1949) Jeffcoate and Roberts (1952) claim that as the angle between the posterior wall of the urethra and the bladder base approaches 180° the closure mechanism is likely to be insufficient Lapides (1958) measured the urethral length and showed that, in the erect position women with stress incontinence had a significantly shortened urethra None of these changes are however constant and leakage may be observed

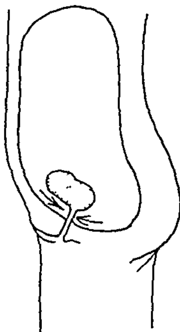


Fig 1 a With a portion of the urethra above the pelvic floor an increase in intra abdominal pressure would not jeopardize closure as the pressure increase would affect this portion of the urethra just as readily as it would the bladder Thus the pressure differential would be unaffected

in a patient where all are absent In some instances no leakage may occur on coughing although all three are present

A recently presented hypothesis explains normal urethral closure at rest and under conditions of suddenly increased intra abdominal pressure (Enhorning 1961) It is based on the supposition that there will be complete closure as long as the pressure in the urethra is higher than that in the bladder By virtue of tonus in the urethral musculature the pressure at rest is presumably higher in the urethra than in the bladder and it can be expected to remain so during a cough or other physical stress provided the increase in intra abdominal pressure is transmitted equally to bladder and urethra (Fig 1 a) If on the other hand the increase in intra abdominal pressure is transmitted more

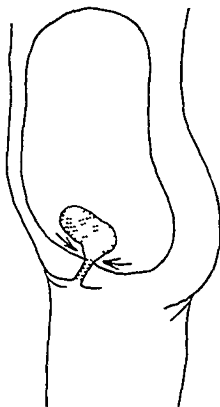


Fig 1 b Closure may be jeopardized, however, if this upper portion of the urethra has become funnel shaped and thus functionally has become a portion of the bladder Then, an increase in intra abdominal pressure could be more readily transmitted to bladder and funnel than to the remaining urethra Thus the pressure differential could decrease to zero

readily to the bladder than to the urethra, intravesical pressure would increase relatively more and could finally become greater than intraurethral pressure (Fig 1 b) If this occurred there would presumably be leakage of urine

The validity of this hypothesis was demonstrated when it was tested in a series of 205 women by simultaneous recording of intra urethral and intravesical pressures Sixty five had stress incontinence, and 140 acted as normal controls Pressure was found to be higher in the urethra than in the bladder in all women relaxing in the lithotomy position When intravesical pressure was raised by coughing intra urethral pressure was simul

taneously increased In the normal controls, in whom coughing provoked no leakage pressure remained higher in the urethra than in the bladder However, in all the women with stress incontinence an increase in intra abdominal pressure was incompletely transmitted to the urethra, and when the cough was vigorous enough to cause leakage there was no point in the urethra where pressure was higher than in the bladder

As age increases, intra urethral pressure decreases (Enhorning 1961) This does not affect complete closure when there is a sudden increase of intra abdominal pressure, provided this pressure is completely transmitted to both the bladder and the upper portion of the urethra —In this paper we describe our experience with a model devised to illustrate the importance of pressure transmittance from the abdominal cavity to the urethra as a mechanism for normal closure

Materials and Method

The bladder urethra model (Fig 2)

The bladder consisted of a two-litre plexiglass container with a lid which could be tightly screwed down It was completely filled with water the pressure of which could be increased by compression of a rubber balloon communicating with the container When the lid had been fixed the only outlet was through the urethra This consisted of a urethra from a female cadaver suspended between two short pieces of thin walled brass tubing each of which went through the centre of circular plexiglass plates 6 cm in diameter One of these was glued to the inside of the bladder lid The plates were fixed together by long screws through the periphery These could be adjusted so that the distance between the plates could be altered to fit the urethral length The whole was enclosed in a rubber tubing which formed a closed space surrounding the urethra Liquid could be injected into this space with a syringe and the pressure regulated to simulate that in the living subject. This pressure substituted for tonus of nonstriated circular musculatur of the urethra

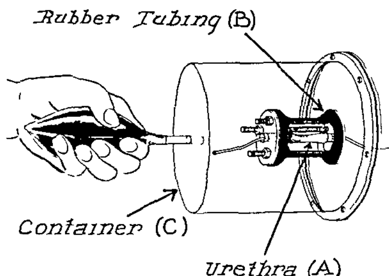


Fig 2 Model to illustrate closure mechanism of female urethra Urethra A, from cadaver, is inside rubber tubing B into which an opening is cut for visualization The tubing is closed at both ends by circular plates Into the space surrounding the urethra thus formed, liquid can be injected Pressure of this liquid is transmitted into the urethra and substitutes for tonus of circular musculature Pressure changes of container C, simulating abdominal cavity and bladder, are transmitted via rubber tubing to urethra Pressures in this organ are recorded via the catheter simultaneously with those in container C

When the model had been assembled, a pressure measurement catheter as previously described (Enhorning, 1960 and 1961), was introduced through the urethra It transmitted intra vesical and intra-urethral pressures to separate electromanometers for simultaneous recording Intra urethral pressures were varied from 20 to 50 cm of water This range was chosen as it is representative for women of 60 years of age or more in whom stress incontinence is most common The model permitted an increase of bladder pressure to 150 cm of water

Results

The catheter could be introduced easily when intraurethral pressure was as low as 20 cm of water Complete closure of the urethra occurred at this pressure because *closure pressure*, i e

the difference between intra urethral and intravesical pressure, was positive When bladder pressure was moderately increased by squeezing the rubber balloon closure pressure remained positive due to transmittance of pressure through the wall of the rubber tubing surrounding the urethra This transmittance was not complete since intra urethral pressure increased slightly less than did intravesical pressure Closure pressure thus continually decreased, finally reaching zero, at which time water could be seen running out of the urethra (Fig 3) As intra urethral pressure increased, the rubber balloon had to be compressed harder to bring closure pressure down to zero and cause leakage When intra urethral pressure had been increased to 50 cm of water closure pressure never fell to zero and leakage was never seen even when bladder pressure was increased to 150 cm of water

Discussion

The bladder urethra model was principally designed to demonstrate that a urethra effects complete closure provided its inside pressure is higher than that in the bladder The model showed an incomplete transmittance of pressure through the rubber wall surrounding the urethra Thus as intravesical pressure increased closure pressure decreased and finally came down to zero When this value was reached leakage was observed The model experiment showed how urethral closure may be maintained because of a passive transmittance of intra abdominal pressure to the urethra and also how leakage occurs when transmittance is incomplete This is considered to be the characteristic insufficiency in stress incontinence

These results obtained with the model resemble those from a study of clinical material (Enhorning 1961) in which it was found that when intra abdominal pressure was raised this was reflected as an increase in both intravesical and intra urethral pressures The funtionally important upper portion of the urethra is above the pelvic floor and under normal circumstances *transmittance* of increased intra abdominal pressure to this part of the organ is complete (Fig 1a) With age the circular musculature

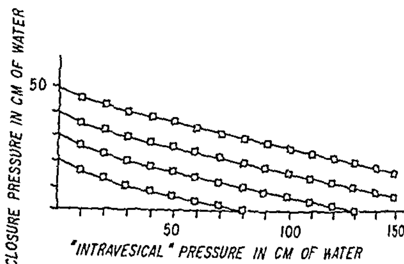


Fig 3 Results of four experiments with changes in intra urethral "tonus" As intravesical pressure i e pressure in container C of Fig 2 increased closure pressure, i e difference between intra urethral and "intravesical" pressure, decreased Closure pressure zero coincided with leakage

of the upper part of the urethra becomes so relaxed as to leave it open The cysto urethrogram will then show a funnel at the bladder urethra junction and measurement of the urethra will show it to be abnormally short (Fig 1 b)

However, even when the intrapelvic part of the urethra has in this way been transformed into a funnel there can still be a good transmittance of intra abdominal pressure to the remaining upper part of the urethra If the tissues marked A in Fig 4 are tense and strong they are able to offer counterpressure to an increase in intra-abdominal pressure and thereby there will be a fairly complete pressure transmittance to the urethra The more the intra-abdominal pressure is increased the more will the urethra be pressed against these tissues If the tissues marked A in Fig 4 are relaxed, on the other hand, the cysto-urethrogram is likely to show a change of the bladder urethra angle as described by Jeffcoate and Roberts (1952) and with such a relaxation an increase in intra abdominal pressure may be offered counter pressure by tissues marked B in Fig 4, thereby allowing only incomplete transmittance of the increased intra abdominal pressure to the urethra

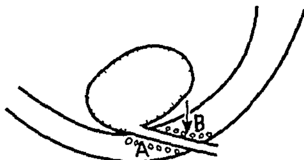


Fig 4 When intra abdominal pressure increases and tissues surrounding urethra move as arrow indicates transmittance of intra abdominal pressure to urethra will depend upon which tissues will be stretched and therefore offer counter pressure those at A or those at B If tissues at A are able to offer effective counter pressure an increase in intra abdominal pressure will be completely transmitted to the urethra If tis ues at A are relaxed and tissues at B offer part of the counter pressure transmittance of intra abdominal pressure to the urethra will be only partial Most operations for stress incontinence give added strength to tissues at A

Treatment probably acts in one of three ways

1 *Drugs*

Intra urethral pressure at rest may be increased by œstrogens (Guercio 1960, Salmon *et al* 1941) or by sympathomimetic drugs (Rashbaum and Mandelbaum 1948, Youssef 1959) In this case the increase in intra abdominal pressure would have to be much greater to bring the difference between intra urethral and intravesical pressure down to zero (Fig 3)

2 *Physiotherapy*

Pelvic exercises may increase muscle tone (Kegel 1948) Voluntary muscles with sphincteric function may thereby become more able to increase intra urethral pressure at a time of stress and thus compensate for an incomplete transmittance of increasing intra abdominal pressure

3 *Surgery*

This may improve transmittance of increasing intra abdominal pressure to the upper portion of the urethra in three ways

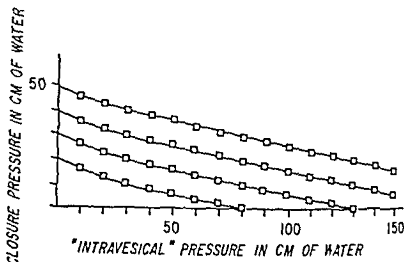


Fig 3 Results of four experiments with changes in intra urethral "torus As intravesical" pressure, i e pressure in container C of Fig 2 increased, closure pressure, i e difference between intra urethral and "intravesical" pressure, decreased Closure pressure zero coincided with leakage

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a The portion of the urethra above the urogenital diaphragm to which intra-abdominal pressure can most readily be transmitted, may be lengthened by plicating sutures (Kelly and Dumm, 1914)

b The tissues of the anterior vaginal wall, posterior to the upper urethra (A in Fig 4), may be strengthened (Marshall Marchetti and Krantz, 1949) and thus able to offer greater counterpressure to the increasing intra abdominal pressure The Kelly (Kelly and Dumm, 1914) and sling types of operation (Aldridge, 1942, Ingelman-Sundberg, 1947, Millin and Read, 1948) probably act in this manner

c Transmittance may be improved by cutting through the tissues marked B in Fig 4 (Ingelman-Sundberg, 1949, Langreder, 1956, Mulvany, 1951) These tissues may be an obstacle to transmittance of intra-abdominal pressure to the urethra

Surgery will only be effective when it causes more complete transmittance from the abdominal cavity to the urethra In the case illustrated in the lowest curve of Fig 3, this is almost complete It is therefore unlikely that surgery would help in such a case The treatment of choice would be medical, the aim being to increase the tonus of the circular musculature of the urethra thus increasing the difference between intra-urethral and intra vesical pressure (upper curve Fig 3)

Simultaneous recording of intravesical and intra urethral pressure directly demonstrates the capability of the urethra to effect closure at a time of increased intra-abdominal pressure, and would be of great value in determining the correct method of treatment in the individual subject

SUMMARY

The importance of equal transmittance of intra abdominal pressure to the urethra and bladder for normal urethral closure is illustrated with a bladder-urethra model The results of incomplete pressure transmittance to the urethra are demonstrated, and the mode of action of treatment discussed

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PLACENTA PRÆVIA AND LOW IMPLANTATION OF THE PLACENTA

BY

USKO NIEMINEN AND ERIK KLINGE

Placenta prævia has always been one of the more serious complications of pregnancy The figures for maternal and fœtal mortality associated with it show that the obstetrician is frequently faced with overwhelming difficulties when dealing with this complication G von Numers (1896) investigated this problem in Finland at the end of the last century Table I shows the situation regarding maternal and fœtal mortality at that time, and at the turn of the century

Although Teräsvuoris (1940) series (Table I) had been collected at a time when the risks associated with Cæsarean section were beginning to diminish and obstetrics generally was making progress, his maternal mortality rate must be regarded as low The larger series investigated by more recent authors, based on cases occurring during the 1940 and 1950 decades, show that the complications associated with placenta prævia have not been fully overcome even in our times Nesbitt (1960) states in his survey that fœtal mortality is commonly still about 15 per cent Macafees (1962) material consisting of 425 cases gave a maternal mortality of 0 5 per cent and a fœtal mortality of 13 1 per cent During the years 1950–1960 in Dublin hospitals out of 1356 patients with placenta prævia six mothers died or 0 44 per cent (O'Driscoll et al 1962)

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USKO NIEMINEN AND ERIK KLINGE

Placenta prævia has always been one of the more serious complications of pregnancy The figures for maternal and fœtal mortality associated with it show that the obstetrician is frequently faced with overwhelming difficulties when dealing with this complication G von Numers (1896) investigated this problem in Finland at the end of the last century Table I shows the situation regarding maternal and fœtal mortality at that time, and at the turn of the century

Although Teräsvuori's (1940) series (*Table I*) [illegible] collected at a time when the risks associated with Cæs[illegible] tion were beginning to diminish and obstetrics [illegible] making progress his maternal mortality rate [illegible] low The larger series investigated by more recent [illegible] on cases occurring during the 1940 and [illegible] the complications associated with placenta [illegible] fully overcome even in our times *Nes*[illegible] survey that fœtal mortality is com[illegible] Macafees (1962) maternal [illegible] nal mortality of 0 5 per cent and [illegible] During the years 1950–1960 [illegible] patients with placenta præv[illegible] (O'Driscoll *et al* 196[illegible])

Table I *Some Statistics Concerning Maternal and Fœtal Mortality Attributed to Placenta Prævia in Finland 1846–1936*

Author	Date	Cases	Maternal Mortality	Fœtal Mortality
G v Numers	1846– 96	61	6 6 %	78 7 %
W Wegelius	1896–1909	78	2 6 %	56 4 %
S Hjelt	1910– 24	118	5 9 %	63 6 %
M Rauramo	1926– 34	113	4 4 %	53 0 %
H Teräsvuori	1925– 36	157	0 6 %	38 9 %

The object of the present study is to examine the problems associated with placenta prævia on the basis of the 420 cases treated during the period 1952–1961 at the I and II Clinics of Obstetrics and Gynæcology, Helsinki University Central Hospital

The Classification and Aetiology of Placenta Prævia

The Development of the placenta in part or entirely in the lower uterine segment is placenta prævia

Placenta prævia should be divided into only two groups

1) Total placenta prævia in which the internal os is entirely covered by the placenta, and

2) Partial placenta prævia in which the internal os is only partially covered by the placenta

The term low implantation of the placenta is used when the internal os is encroached on by the placenta so that the placental edge can be palpated with a finger introduced through the cervix, but the placenta does not extend beyond the margin of the internal os (Greenhill, 1960)

Martius (1962) states that, in so far as the placental tissue does not appear at the internal os and not until later is it evident that the placenta is located in the lower uterine segment, the term insertio depressa placentæ should be used This relationship may change to placenta prævia as the cervix dilates and the degree

Fig 3 The effect of prostaglandin E_1 on the longitudinal musculature of 4 segments of equal lengths from the human Fallopian tube defined according to Fig 2 Case 480 Age 50 years Postmenopausal group

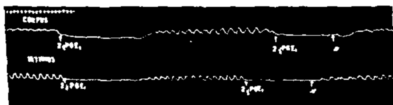


Fig 4 The effects of prostaglandin E on the uterus Case 500 Age 36 years Proliferatory phase

of the distal part of the tube as the organ was always cut into four parts of equal length

The effects exerted by prostaglandin E_1 demonstrated in this paper correspond well to those produced by prostaglandin" a

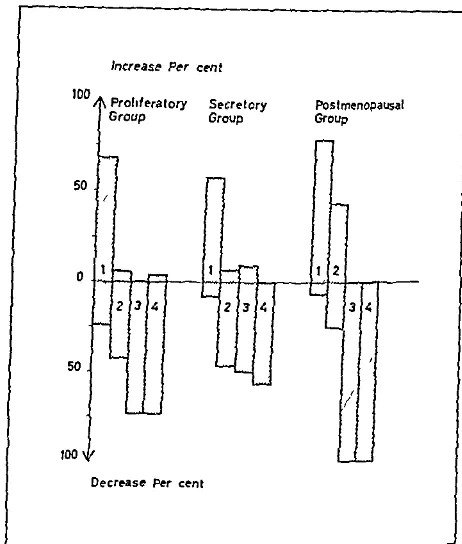


Fig 5 The changes in tonus, caused by prostaglandin E_1, in the segments 1–4 of the Fallopian tubes from the three groups of women

concentrate of the lipid soluble acidic material of human semen (Eliasson, 1959), tested on the Fallopian tube (Sandberg *et al*, 1963) and on the uterus (Eliasson, 1959)

The physiological significance of the apparently specific action of prostaglandin E_1 might be to promote the fertilization of the ovum The following working hypothesis is suggested

From the seminal pole in the posterior fornix prostaglandin

of the placenta prævia may change during the same process Martius divides placenta prævia into the following three forms

1) Placenta prævia totalis,

2) Placenta prævia partialis, and

3) Placenta prævia marginalis, in which the placenta remains at the edge of the internal os without extending to the opening

It is evident from the foregoing that methods of grouping are not entirely comparable Some authorities use classifications still diverging from these and discounting *insertio depressa placentæ* These dissimilarities considerably affect the results presented in different material, thus making comparison difficult

The ætiology of placenta prævia is not yet fully understood The opinion quite commonly held is that the factor decisively giving rise to placenta prævia is the prevention of implantation of the ovum in the fundus and corporeal areas Disturbances of endometrial activity may be caused by infection, several pregnancies, abortions, curettage submucous myomas, uterine structural anomalies and endometrial atrophy or hyperplasia arising from various causes Nidation of the ovum may also have been disturbed

Granzow (1944) in his article further mentions such ætiological factors as the mother's constitution hypoplasia of the genitalia endocrine (mostly thyroidal) disturbances and heredity

Iffy (1962) is of the opinion that the implantation of the ovum *in the lower* uterine segment derives from faulty hormonal *activity* His view is that placenta prævia is often preceded by delayed ovulation when luteal influence would have been weaker than normal The result of this would be an extra or at least a subclinical menstruation notwithstanding the conception The ovum becomes detached from its nidus and is shifted by the effects of the flow and by gravidity nearer the internal os, to be implanted afresh In such a case it is possible that an undiagnosed abortion may occur Another reason for the hæmorrhage displacing the ovum could be the microscopically demonstrable fact that even normally vaso constriction and extravasation may occur in the endometrium around the fertilized ovum from 27 to 35 days after the last menstruation Iffy (1962) finds further support for his theory by showing that in his series 60 per cent of the placenta

Table II *Earlier Complications Possibly Causing Endometrial Defects in our 420 Patients*

One abortion	103	(24 5 %)
Several abortions	61	(14 5 %)
Puerperal infection	16	(3 8 %)
Cæsarean section	30	(7 1 %)
Placental retention	13	(3 1 %)
Placenta prævia	6	(1 4 %)
	229	(54 4 %)

prævia babies are heavier at the 38th week of the pregnancy than normal babies The reason for this is that they would be on an average three weeks older than assumed, since fertilization had occurred prior to the last flew The remaining 40 per cent are nearer to normal in weight for the reason, according to Iffy, that the presumed additional menstruation had remained sub clinical

Iffy s theory seems possible in certain cases, but hardly acceptable in general In our own material we endeavoured to find factors causing disturbance of endometrial activity indicated in the patients anamneses The results are given in Table II

The figures presented in this table support the suggestion that those factors damaging the endometrium in the corporeal areal create favourable conditions for the occurrance of placenta prævia for a factor of this kind is recorded in a total of 54 4 per cent of the cases

Frequency

The incidence of placenta prævia, according to different reports, varies between 0 1 per cent and 1 0 per cent This dissimilarity is influenced not only by the above-mentioned different methods of classifying placenta prævia but also by diagnostic procedures, diagnostic criteria and geographical variations According to Nesbitt (1960) the average frequency is 0 53 per cent The number of births dealt with at the I and II Clinics of Obstetrics and Gynæcology, Helsinki University Central Hospital, between 1952 and 1961 was 73,605, of which 420 cases were either placenta prævia

Table III *Age*

Under 20 years	13	(3 1 %)
20–29 years	180	(42 8 %)
30–39 years	185	(44 1 %)
More than 39 years	42	(10 0 %)
	420	

Table IV *Parity*

Primigravidæ	109	(26 0 %)
2 to 4	253	(60 2 %)
5 and over	58	(13 8 %)
	420	

or insertio depressa placentæ In all cases comprising our material the duration of the pregnancies was at least six months The classification method proposed by Martius is the method chiefly used in our clinics The material is divided into two 5 year periods 1952–1956 and 1957–1961 in order to ascertain how the methods of treatment of mothers and babies practised in the last five years had affected the results

The incidence frequence for the first 5 year period is 0 66 per cent and the second 0 48 per cent while that of the whole series is 0 57 per cent If we exclude the cases of insertio depressa placentæ which totalled 85 we obtain a placenta prævia frequency of 0 46 per cent (0 46 per cent from the first 5 year period and 0 45 per cent from the second)

Table III shows how the cases are divided among the different age groups

In our material the number of mothers aged under 20 is about one third (*i e* 3 1 per cent) of that of mothers, aged 40 and over (10 per cent) In average materials however there are more mothers under 20 years of age than over 39 Soininen (1961)

Table IV presents the gravidity status of the mothers

There are 26 per cent primigravidæ and 74 per cent multigravidæ in our series According to Martius (1962) there are generally about five times more multigravidæ than primigravidæ patients in placenta prævia series

Table V shows the degree of the placenta prævia and the number of insertio depressa placentæ cases occurring in our series

It should be noted that it is sometimes difficult to classify the different degrees especially those of minor development Further the degree of placenta prævia may change during delivery and then the time at which the placenta prævia was verified will

Table V *The Incidence of the Different Types of Placenta Prævia for the Two 5 Year Periods*

Degree of Pl Prævia		1952–1956		1957–1961
Pl pr totalis		64 (25 8 %)		90 (52 6 %)
Pl pr partialis	173	73 (29 4 %)	162	45 (26 3 %)
Pl pr marginalis		36 (14 2 %)		27 (15 8 %)
Insertio depressa pl		76 (30 6 %)		9 (5 3 %)
Total		249		171

determine the degree of the case Of late, marginal sinus rupture has become more generally known, the bleeding from which may previously have been put down to placenta prævia (Ferguson, 1955, Jarvinen and Nieminen, 1962) The observation that insertio depressa placentæ was diagnosed in only 5 3 per cent of patients in the second series compared with 30 6 per cent in the first suggests that the accuracy of diagnosis improved during the later years

Clinical diagnosis

The classical early symptoms of placenta prævia include vaginal bleeding of a bright red colour, commencing with or without moderate pain The bleeding usually starts in the last months of the pregnancy or at the onset of labour Even slight uterine contractions may separate placental tissue from the wall of the lower segment because the placenta cannot follow the movements of the uterus The amount of bleeding is variable and is not always related to the degree of the placenta prævia, in other words, hæmorrhage associated with placenta prævia marginalis may be more profuse than that with placenta prævia totalis The loss may be continual or episodic In contrast uterine contraction is persistent in patients with abruptio placentæ Table VI shows the time of the first hæmorrhage in our series

Bleeding first appeared two weeks or more prior to term in 57 9 per cent of the cases and in 33 1 per cent at or near term In 9 per cent the time of onset of bleeding was not established

Table VI First Sign of Bleeding

More than 3 months before term	95	(22 7 %)
3 to 2 months before term	54	(12 8 %)
2 to 1 month before term	44	(10 5 %)
4 to 2 weeks before term	50	(11 9 %)
2 weeks or less differing from term	139	(33 1 %)
unknown	38	(9 0 %)
	420	

In cases where hæmorrhage is not very profuse, the diagnosis may be confirmed radiologically The method developed by Johanson (now Unnerus) has been used in our Clinic with good results in recent years (Johanson and Viikeri, 1956) One anteroposterior and one lateral film is taken, using the appropriate filter and compression By this method, accuracy in diagnostic localization of the placenta is over 99 per cent High positioning of the presenting part or deviation from the longitudinal axis, may be observed in the X ray picture In addition to the placenta, the presenting part may also be displaced by a full bladder or rectum a pelvic tumour, hæmatoma, pelvic anomalies or a large pelvis Cystographs or rectographs give uncertain results while amniographs may be dangerous to the fœtus Angiographs are reliable but up to the present too inconvenient for routine use

In Macafees (1962) series the position of placenta was noted as being posterior in 53 8 per cent of the cases observed, anterior in 30 2 per cent and anteroposterior in 16 per cent Placenta prævia often extends over a wider area than normal, probably because its location offers poorer nutritional possibilities than normally The placenta is then also thinner and more lobulated than normal

From the point of view of clinical diagnosis it is notable that placenta prævia often results in abnormal fœtal lies as shown in Table VII

The frequency of transverse and oblique lies (13 6 per cent) is notable In general transverse and oblique lies occur in about 0 5 per cent of all cases Breech presentation occurred in 8 6 per cent of patients some three times more often than normally

In all patients with hæmorrhage an internal examination must be carried out and this should be done only in a hospital where

Table VII *Fœtal Lies*

Vertex	327	(77.8%)
Breech	36	(8.6%)
Transverse	47	(11.2%)
Oblique	10	(2.4%)
	420	

Table VIII *Mode of Diagnosis*

Radiological	118	(28.1%)
Vaginal examination	142	(33.8%)
Rectal examination	7	(1.7%)
Cæsarean section	76	(18.0%)
Clinical symptoms and inspection of the placenta	77	(18.4%)
	420	

blood transfusion and operative or surgical facilities are immediately available. Rectal examination gives only an incomplete picture of the situation and may increase the hæmorrhage. According to Nesbitt (1960) fatal pre-natal hæmorrhages are almost always the result of manipulation. The more valuable diagnostic methods are thus internal examination, and, where the situation permits, radiology.

Anamnestic information, the clinical picture and subsequent inspection of the placenta complete the diagnosis, together with a visual and palpatory examination if Cæsarean section is performed. In table VIII we show how placenta prævia and insertio depressa placentæ were clinically confirmed in our material.

When considering the differential diagnosis the various factors giving rise to bleeding should be borne in mind, such as ablatio placentæ ante tempus, ruptura sinus marginalis placentæ, tumor portionis and – cervicis uteri, cervicitis, erosio portionis, colpitis, varices vulvæ et vaginæ, hæmorrhoides, hæmaturia, polypus urethræ etc. Generally speaking, a careful clinical examination will establish the reason for the bleeding. In those cases where a diagnosis of placenta prævia has been eliminated radiologically, one should always consider a speculum examination to determine the cause of the bleeding.

The treatment of placenta prævia and insertio depressa placentæ

There is no consistent course in the treatment of cases of placenta prævia, but each case must be considered individually. The following factors should be taken into account in the examination of the patient:

The extent of the bleeding
The stage of dilatation of uterine os
The degree of the placenta prævia
The fœtal membranes and condition of the fœtus

It is generally accepted that a Cæsarean section be carried out if bleeding is profuse and the uterine os is closed or only slightly open Similarly, section is performed in all cases of placenta prævia totalis In such instances, section is the only method of assuring rapid and safe treatment in a situation dangerous to both mother and child

According to different authors and taking all forms of placenta prævia into consideration, the frequency of Cæsarean section nowadays lies between 60 per cent and 90 per cent Yet only some ten years ago the frequency was very much lower, varying between 14 per cent and 75 per cent, according to the data collected by Colvin (1952)

Opinions about the use of section in placenta prævia partialis and marginalis are by no means unanimous Gauss (1953) favours a conservative line and in his opinion section in such cases is never necessary for the mother and seldom for the child Martius (1962) supports active treatment especially in cases of profuse bleeding and this applies also to many other authors (Grant 1955 Manly 1958) Vara (1952 and 1958) holds the view that the correct method of treatment is to be found between these extremes and each case must be decided individually, taking into account the condition of both mother and child

In acute cases where there is severe bleeding together with uterine contractions and where the baby has either succumbed or is in a weak condition every effort must be concentrated on saving the mother Here the best method of treatment is section Nevertheless this does not mean that conservative treatment is to be overlooked if it entails no danger to the mother Depending on the degree of cervical dilatation various possibilities may then arise in the management of the case such as rupture of the membranes tamponade with the aid of Willet Gauss forceps traction by vacuum etxractor or internal version and leg traction

Conservative management is appropriate if bleeding is minor and if labour has not begun It is then important to treat the

mother's anæmic condition by blood transfusion, since prolonged bleeding, even though not copious, will give rise to anæmia in the fœtus and to fœtal asphyxia Goltner and Österlund (1961) have demonstrated that administering iron to the mother increases the ferritin content of the placenta, this having great importance in the iron resorption via the placenta to the fœtus As well as additional blood, the mother should be given iron if she requires prolonged treatment for anæmia Bleeding in placenta prævia may in part derive from the fœtal circulation and in the worst event may result in the birth of an exsanguinated baby (Neligan and Russel 1954, Wasz-Hockert *et al* 1956, and Widholm 1958) Fœtal asphyxia may also be due to pressure of the presenting part on the placenta or on the site of the cord insertion in the placenta

If maternal symptoms do not demand immediate measures, particular attention should be paid to the state of the fœtus The pregnancy should be maintained as near to term as possible, since the prognosis for a premature baby involved in even minor complications is worse than that of full-term infant (Macafee *et al*, 1962, Nesbitt 1960, and Semmens, 1959) Should the fœtus exhibit even the slightest sign of asphyxia, Cæsarean section should be resorted to, even though the delivery might be effected by normal means without danger to the mother After favourable conservative treatment, section should be carried out at the onset of labour, since there is no point in jeopardizing the results of prolonged conservative treatment by subjetcing the case to the possible complications associated with vaginal delivery

Table IX presents the period of gestation at the time of birth in our series

In all, 53 9 per cent of the labours were premature Post term deliveries occurred in only 2 1 per cent

In Table X the results of treatment are summarized for each year together with a break-down in relation to birth weight groups

Altogether, 270 cases were treated by Cæsarean section, or 64 3 per cent In the first 5-year period there were 133 sections (53.4 per cent) and in the second 137 (80 0 per cent) The corresponding figures for vaginal deliveries are 150 (35 7 per cent),

Table IX. *Time of Birth*

More than 2 months before term	45 (10 7%)
2 to 1 month before term	86 (20 5%)
1 month to 2 weeks before term	95 (22 7%)
2 weeks or less differing from term	185 (44 0%)
More than 2 weeks after term	9 (2 1%)
	420

Table X. *Annual Results Obtained in Cases of Placenta Prævia and Insertio Depressa Placentæ*

Year	Number of Births	Number of Pl Pr and In Depr Pl		≧2500 g		1250–2499 g		≦1249 g	
		Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
1952	7072	37	9	25	—	12	4	—	5
1953	7240	43	10	33	1	10	6	—	3
1954	7759	46	8	27	4	17	2	2	2
1955	7731	50	11	43	—	7	7	—	4
1956	8044	30	5	24	2	6	1	—	2
1952 1956	37846	206	43 (17 3%)	152	7	52	20	2	16
1957	8290	27	8	14	3	6	3	2	2
1958	,613	37	11	34	3	3	4	—	4
1959	7810	30	12	22	5	8	6	—	1
1960	6470	21	4	15	—	6	3	—	1
1961	5646	21	5	19	—	2	3	—	2
1957 1961	35759	131	40 (23 4%)	104	11	25	19	2	10
1952 1961	73605	337	83 (19 7%)	256	18	77	39	4	26

Table XI *Results in Cases of Placenta Prævia of Various Degrees Treated by Cæsarean Section The Results are Further Divided by Birth Weight*

Degree of Pl P	≧2500		1250–2499 g		≦1249		Total	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Pl pr totalis	89	8	26	18	—	7	115	33 (22 3%)
Pl pr partialis	43	4	14	6	2	4	59	14 (19 2%)
Pl pr marginalis	19	—	8	1	—	—	27	1 (3 5%)
Ins depr pl	17	—	3	1	—	—	20	1 (4 8%)
Total	168	12	51	26	2	11	221	49 (18 2%)

116 (46 6 per cent) and 34 (20 0 per cent) Table XI shows the results obtained in patients with different degrees of placenta prævia treated by section

mother's anæmic condition by blood transfusion, since prolonged bleeding, even though not copious, will give rise to anæmia in the fœtus and to fœtal asphyxia Goltner and Österlund (1961) have demonstrated that administering iron to the mother increases the ferritin content of the placenta, this having great importance in the iron resorption via the placenta to the fœtus As well as additional blood, the mother should be given iron if she requires prolonged treatment for anæmia Bleeding in placenta prævia may in part derive from the fœtal circulation and in the worst event may result in the birth of an exsanguinated baby (Neligan and Russel 1954, Wasz-Hockert *et al* 1956, and Widholm 1958) Fœtal asphyxia may also be due to pressure of the presenting part on the placenta or on the site of the cord insertion in the placenta

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down from its oblique breech position by entry through the placenta after which the placenta was separated manually and the uterine cavity curetted The patient died soon after these measures rupture of the lower uterine segment being confirmed at necropsy During treatment the patient was given fluid and blood transfusions

Case No 3 (1955) 27 year-old III gravida The patient was suffering from placenta prævia partialis Pregnancy was 6 weeks premature High blood pressure was confirmed also severe albuminuria (4 5 pro mille) As the patient was bleeding fairly profusely both legs of the fœtus which presented by the breech were brought down and the fœtus was extracted Manual separation of the placenta was also carried out. Rupture of the lower uterine segment occurred during the manipulation and this was sutured per vaginam Uterine tamponade was also performed The profuse bleeding continued but hysterectomy was not carried out until several hours had elapsed The patient died of uræmia 5 days after the operation Altogether 20 flasks of blood were administered to the patient who also received Macrodex® (Leiras) and the propriate treatment for uræmia

Examining these cases in retrospect it seems likely that the first patient could have been saved by carrying out an immediate hysterectomy since the uterus had not contracted in spite of medication In the second case, the patient would probably have been saved if a Cæsarean section had been performed immediately Similarly section or hysterectomy done in time would evidently have led to a better result in the third case However, it is to be noted that in the third case the hæmorrhage could have been attributable to afibrinogenæmia – a disease which in 1955 was not generally known

When one considers that in our clinic which enjoys ideal facilities and conditions for the treatment of maternity patients some 10 per cent of the total deliveries of the whole country were treated during the period under review it is very probable that several maternal deaths in Finland could have arisen from placenta prævia during that time

On examining more closely these factors having significance in preventing maternal mortality it is evident that a patient developing hæmorrhage in the third trimester should always be taken to a hospital in which the best possible facilities for diagnosis and for treatment of mother and new born child are available If bleeding is profuse plasma or Macrodex infusion should be administered to the patient at once and blood transfusion given after

Table XII *Results of Placenta Prævia of Various Degrees Delivered Vaginally The Results are Further Divided by Birth Weight*

Degree of Pl Pr	≧2500 g		1250–2499 g		≦1 49 g		Total	
	Alive	Dead	Alive	Dead	Alive	Dead	Alive	Dead
Pl pr totalis	—	1	2	1	—	2	2	4 (66 7%)
Pl pr partialis	18	3	7	9	—	8	25	20 (44 4%)
Pl pr marginalis	22	1	7	2	1	2	30	5 (14 3%)
Ins depr pl	48	1	10	1	1	3	59	5 (7 8%)
Total	88	6	26	13	2	15	116	34 (22 7%)

Table XII gives the results of cases of placenta prævia of different degrees, delivered vaginally

In making a comparison between placenta prævia treated by section and those dealt with vaginally it is observed that for all degrees of placenta prævia the Cæsarean section results are considerably better

Blood transfusion had to be given in a total of 111 cases and 76 patients were given both blood transfusion and fluid infusions 26 patients were given only fluid infusions

Maternal mortality

During the 5 year period between 1952–1956 three maternal deaths occurred in 249 births complicated by placenta prævia The maternal mortality rate for this period is thus 1 20 per cent No maternal death occurred during the 5 year period 1957–1961, during which time 171 cases were treated The maternal mortality rate for the whole series, comprising 420 cases is thus 0 71 per cent

Case No 1 (1952) 25 year old II gravida confirmed placenta prævia partialis The pregnancy was at term and fœtus presented by the breech The patient bled profusely during section owing to uterine atony She was given blood transfusion and suitable drugs to ensure uterine contraction Death occurred 25 minutes after the operation At necropsy it was found that bleeding had continued within the uterus

Case No 2 (1953) 26 year old II gravida suffering from a diagnosed placenta prævia totalis The pregnancy was over 2 months premature The patient had bled profusely on the way to the hospital but the blood pressure was still 120/80 when treatment was instituted The fœtus was at once brought

6) Too active attempts at vaginal delivery may result in fœtal injury or loss

The comparison of infant mortality figures presented in different series is difficult – often completely impossible, because precise distinctions between mature, premature and immature infants are not always made Sometimes the immature infants are excluded altogether The real danger constituted by placenta prævia can be demonstrated by reporting fœtal loss at every stage of maturity By excluding the immature infants one can determine the pos ibilities inherent in various methods of treatment for saving otherwise viable babies

Table X shows that in our series there were 274 mature infants ($\geq$2500 gr) or 65 4 per cent, 116 premature infants (1250–2499 gr) or 27 6 per cent and 30 immature infants ($\leq$1249 gr) or 7 per cent Total perinatal mortality amounted to 83 (19 7 per cent) of which 26 are immature Thus the mortality rate in mature and premature infants was 14 6 per cent (57 cases) When we examine the mortality in respect to mature and premature infants for the two 5 year periods, we find that the figure between 1952–1956 was 27 (11 7 per cent) and between 1957–1961 30 (18 9 per cent)

Table XIII gives the immediate cause of death of 57 mature and premature infants ascertained either from clinical examination or at necropsy

Table XIV gives the mortality in respect of mature and premature infants in relation to the type of placenta prævia and table XV presents the fœtal position immediately before birth

It is evident that child is in greatest danger in cases of placenta prævia totalis and placenta prævia partialis, for 87 8 per cent of the dead babies belonged to these groups Since placenta prævia totalis and partialis were abundantly represented in these cases abnormal fœtal lies were relatively more numerous than in the series as a whole (Table VII and XV)

It will be seen from tables XI and XII that in the 57 mature and premature deaths 38 were treated by section (66 7 per cent) In table XVI we set out the different methods employed in 19 cases delivered vaginally

Of the above mentioned 57 instances of fœtal death 29 (50 9

cross-matching Rectal examination should not be attempted. Vaginal examination should only be carried out in hospitals equipped for blood transfusion and section

When once the diagnosis of placenta prævia has been confirmed, the patient must in no circumstances be allowed to leave *the hospital before delivery This rule must also be remembered* in these cases in which placenta prævia has been discovered by chance from X-ray pictures, no bleeding having occurred

The danger of uterine rupture is great in all active obstetric manœuvres per vaginam In association with placenta prævia the danger of atony of the lower uterine segment is greater than normally (Macafee *et al* 1962) In the rare cases of cervical insertion of the placenta, the possibility of placenta accreta and atony is considerable (Greenhill, 1960, Schroderus, 1949), likewise in the even rarer incidence of cervical pregnancy (Turunen, 1962 and 1963) It is highly probable that placenta accreta is more general in connection with placenta prævia than in cases not so complicated The early recognition of such factors and recourse to hysterectomy without delay may frequently result in saving the mother's life

Infant mortality

In a pregnancy complicated by placenta prævia the life of the infant may be in jeopardy principally for the following reasons

1) A low-lying placenta frequently gives rise to premature birth

2) In the last stages of the pregnancy, or during delivery, the presenting part compresses the placenta or the cord at its insertion point, causing fœtal asphyxia

3) Unfavourable location of the placenta provokes disturbances in its development Such disturbances may prove dangerous for the fœtus, particularly in the final stage of the pregnancy or in labour

4) The placenta may become partially detached, causing fœtal asphyxia due to bleeding

5) Damage of the placenta at the onset of labour, may result in rupture of vessels of the chorionic villi or of the larger placental vessels resulting *in bleeding from the fœtal circulation*

6) Too active attempts at vaginal delivery may result in fœtal injury or loss

The comparison of infant mortality figures presented in different series is difficult – often completely impossible, because precise distinctions between mature, premature and immature infants are not always made Sometimes the immature infants are excluded altogether The real danger constituted by placenta prævia can be demonstrated by reporting fœtal loss at every stage of maturity By excluding the immature infants one can determine the possibilities inherent in various methods of treatment for saving otherwise viable babies

Table X shows that in our series there were 274 mature infants (≥2500 gr) or 65 4 per cent, 116 premature infants (1250–2499 gr) or 27 6 per cent and 30 immature infants (≤1249 gr) or 7 per cent Total perinatal mortality amounted to 83 (19 7 per cent) of which 26 are immature Thus the mortality rate in mature and premature infants was 14 6 per cent (57 cases) When we examine the mortality in respect to mature and premature infants for the two 5 year periods, we find that the figure between 1952–1956 was 27 (11 7 per cent) and between 1957–1961 30 (18 9 per cent)

Table XIII gives the immediate cause of death of 57 mature and premature infants ascertained either from clinical examination or at necropsy

Table XIV gives the mortality in respect of mature and premature infants in relation to the type of placenta prævia and table XV presents the fœtal position immediately before birth

It is evident that child is in greatest danger in cases of placenta prævia totalis and placenta prævia partialis for 87 8 per cent of the dead babies belonged to these groups Since placenta prævia totalis and partialis were abundantly represented in these cases, abnormal fœtal lies were relatively more numerous than in the series as a whole (Table VII and XV)

It will be seen from tables XI and XII that in the 57 mature and premature deaths 38 were treated by section (66 7 per cent) In table XVI we set out the different methods employed in 19 cases delivered vaginally

Of the above mentioned 57 instances of fœtal death, 29 (50 9

cross-matching Rectal examination should not be attempted Vaginal examination should only be carried out in hospitals equipped for blood transfusion and section

When once the diagnosis of placenta prævia has been confirmed, the patient must in no circumstances be allowed to leave the hospital before delivery This rule must also be remembered in these cases in which placenta prævia has been discovered by chance from X-ray pictures, no bleeding having occurred

The danger of uterine rupture is great in all active obstetric manœuvres per vaginam In association with placenta prævia the danger of atony of the lower uterine segment is greater than normally (Macafee *et al* 1962) In the rare cases of cervical insertion of the placenta, the possibility of placenta accreta and atony is considerable (Greenhill, 1960, Schroderus, 1949), likewise in the even rarer incidence of cervical pregnancy (Turunen, 1962 and 1963) It is highly probable that placenta accreta is more general in connection with placenta prævia than in cases not so complicated The early recognition of such factors and recourse to hysterectomy without delay may frequently result in saving the mother's life

Infant mortality

In a pregnancy complicated by placenta prævia the life of the infant may be in jeopardy principally for the following reasons

1) A low-lying placenta frequently gives rise to premature birth

2) In the last stages of the pregnancy or during delivery, the presenting part compresses the placenta or the cord at its insertion point, causing fœtal asphyxia

3) Unfavourable location of the placenta provokes disturbances in its development Such disturbances may prove dangerous for the fœtus, particularly in the final stage of the pregnancy or in labour

4) The placenta may become partially detached causing fœtal asphyxia due to bleeding

5) Damage of the placenta at the onset of labour, may result in rupture of vessels of the chorionic villi or of the larger placental vessels resulting in bleeding from the fœtal circulation

latter period is much greater than that of the first However, in actual fact, no increase in mortality occurred In the period 1952–1956 there appears a total of 76 cases of insertio depressa placentæ having a favourable prognosis, whereas for the period 1957–1961 there are only 9 such cases The relative incidence of true placenta prævia for both 5 year terms are almost equal–173 and 162, the frequency figures thus being 0 46 per cent and 0 45 per cent During 1952–1956 the losses in respect of mature and premature infants in true cases of placenta prævia amounted to 25 altogether, between 1957–1961 there were 29, *mortality rates of* 15 9 per cent and 19 1 per cent respectively

In the second period there were 5 cases of intra uterine death prior to admission to hospital and in the first period 2 such instances By analysing the fœtal mortality (Table XIII) by cause of death, the above mentioned disparity could be further equalised but probably this is not worthwhile On the basis of the foregoing it is to be concluded that in spite of improved surgical facilites and better pædiatric care, the fœtal mortality rate over recent years has not diminished

It is improbable that infant mortality will be greatly lowered by the change over of present-day methods of management The preparation for every operative delivery takes time, and, even if treatment can be commenced immediately after the mother s arrival at hospital it may still be too late to save the baby s life The journey to the hospital takes valuable time and the transportation often aggravates the bleeding It is therefore important that a diagnosis of placenta prævia be made in good time Even in the case of a minimal bleeding occurring *in* the last *trimester*, the possibility of this being attributable to placenta *prævia must* be taken into account during examination By the use of the X ray diagnostic methods mentioned earlier the exact placental position can be established with certainty In all fœtal and pelvic X ray examinations carried out in the final stage of pregnancy the localisation of the placenta must be ascertained If placenta prævia is confirmed, the patient should be conveyed *to* hospital immediately where treatment should be continued right up to the time of delivery Treatment of a patient in hospital can be more expeditious and the possible occurrence of hæmorrhage from the fœtal

Table XIII *Principal Cause of Death of Dead (Premature and Mature) Infants*

Diagnosis	1952–1956	1957–1961
Prematurity and asphyxia	11	3
Prematurity	6	2
Pulmonary atelectasy and prematurity	2	5
Pulmonary atelectasy	–	5
Anemia	2	1
Pulmonary and/or cerebral bleedings	1	3
Intrauterine death	2	5
Abnormalities	1	2
Hyaline membrane	1	1
Abruptio placentæ	–	1
Rhesus incompatibility	–	1
Pneumonia	1	–
Prolapse of the umbilical cord	–	1
	27	30

Table XIV *Degree of Placenta Prævia of Dead (Premature and Mature) Infants*

Pl pr totalis	28	(49 2 %)
Pl pr partialis	22	(38 6 %)
Pl pr marginalis	4	(7 0 %)
Insertio depressa pl	3	(5 2 %)
	57	

Table XV *Fœtal Lies of Dead (Premature and Mature) Infants*

Vertex	37	(64 8 %)
Breech	12	(21 2 %)
Transverse	5	(8 8 %)
Oblique	3	(5 2 %)
	57	

Table XVI *Mode of Vaginal Delivery of Dead (Premature and Mature) Infants*

Rupture of the membranes	14
Assisted breech	2
Leg brought down	2
Forceps	1
	19

per cent) were treated as emergency cases, i e within 48 hours of their admission into hospital The other cases were at first treated conservatively for various periods of time

When comparing the incidence of fœtal mortality for the two 5-year periods it seems astonishing that the percentage for the

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circulation will be minimal In the case of insertio depressa placentæ it is sufficient if the situation is explained to the mother and she is advised to go to the hospital at the commencement of even minor flow or pain

SUMMARY

In their study the authors have discussed the ætiology, incidence and treatment of placenta prævia and insertio depressa placentæ, *as well as maternal and fœtal* mortality The authors present a series comprising 420 cases from the I and II Clinics of Obstetrics and Gynæcology, Helsinki University *Central Hospital during* the period 1952–1961 Altogether, 73,605 births were dealt with during this period, thus giving the incidence for placenta prævia and insertio depressa placentæ of 0 57 per cent If we exclude the cases of insertio depressa placentæ we obtain an incidence of 0 46 per cent For purposes of comparison, the series is divided into two 5 year periods, 1952–1956 and 1957–1961 Maternal mortality for the first period was 1 20 per cent (3 cases) and nil in the second A total of 83 babies was lost (19 7 per cent) Taking into account only mature ($\geqq$2500 gr), and premature infants (1250–2499 gr) the mortality rate stood at only 14 6 per cent In so far *as fœtal mortality is based only on cases of placenta prævia totalis,* partialis, and marginalis, the figure becomes 23 3 per cent (the figure for mature and premature infants being 16 4 per cent)

Placenta prævia is still a serious complication of pregnancy constituting hazards for both mother and child It is evident that, even with the most effective management, the fœtal mortality rate will not be greatly improved On the other hand, maternal mortality is virtually always *avoidable It appears that the only means* of diminishing the fœtal mortality is to ensure the diagnosis of placenta prævia well before an acute phase has developed On confirmation of placenta prævia the mother should be conveyed to hospital for treatment, which should be continued until delivery In acute situations, the best method of delivery is by Cæsarean section ,the use of which is also on the increase in cases of placenta prævia of less urgency

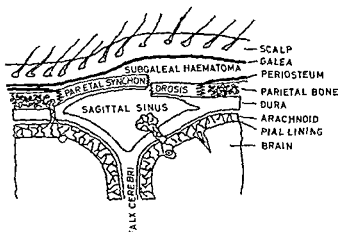


Fig 1 Subgaleal hæmatoma between scalp and crown of skull The size of the hæmorrhage suggests the pre ence of substantial source of bleeding

Previous publications have indicated a correlation between subgaleal hæmatoma and instrumental delivery but have not considered the possible significance of other obstetrical factors in the causation of the condition The present material consists of four cases with death of the child in two In two cases delivery was spontaneous and in the remaining two it was completed by VE extraction The cases presented below occurred in 1962 at the Departments of Obstetrics and Gynæcology in Gothenburg with about 6 000 deliveries per year

Case Reports

Case 1 (90163/62)

Obstetric A 28 year old primigravida Spontaneous delivery at full term It was remarkable however that the caput succedaneum became very marked and extended to the floor of the pelvis whilst the fœtal head was still high in the birth canal The patient also exhibited very marked uterine activity

Pædiatric Birth weight 3 390 gm The child was asphyctic but soon re covered after routine toilet of the upper airways However the child soon became pale and within half an hour it was transferred to the Department of Pædiatrics for observation The child had a large œdematous and fluc tuating swelling at the back of the head Palpation also suggested a deep depression of the occipital bone Respiration became irregular and the heart

Lehmann O Andersson H Hansson G Malmström T and Ryba W Acta obst et gynec scandinav 42 358 1963

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POST-NATAL SUBGALEAL HÆMATOMAS

BY

LEHMANN O ANDERSSON H HANSSON G MALMSTRÖM T AND RYBA W

Cephalhæmatomata are situated under the periosteum and limited to the corresponding part of the skull whilst subgaleal hæmatomata are situated between the galea and the vault of the skull (Fig 1) Subgaleal hæmatomata are able to dissect their way diffusely over the entire roof of the skull Some of the subgaleal blood tends to coagulate rapidly and changes palpated in the scalp can be *misinterpreted as local œdema of the scalp* No initial discoloration of the skin occurs, and it is remarkable that digital depressions form on pressure very easily Another typical finding is a fluctuation owing to a subgaleal accumulation of liquid blood

A considerable amount of blood may collect and spread over a large surface without producing any conspicuous change in the configuration of the fœtal head For the child this may imply a heavy loss of blood, which remains undiagnosed and which gradually *results in hæmorrhagic shock threatening life* In some cases such loss of blood has proved lethal

A few fatal cases of such *subgaleal extracranial hæmorrhages* have been published and ascribed to trauma associated with delivery Obstetric operations with the Vacuum Extractor have been held responsible for these fatal cases of post natal subgaleal hæmatoma (Felding, 1960, Lange, 1961)

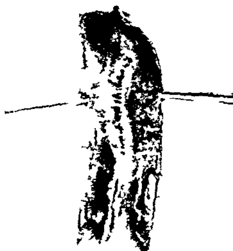


Fig 3 Case 1 Autopsy revealed a large subgaleal hæmatoma and a 3—4 cm long rupture of the interparietal synchondrosis Rupture verified microscopically

rate increased. In the course of the first day of life generalised convulsions of both tonic and clonic character occurred The child died 32 hours after birth.

Skull X ray 4 hours after birth (Fig 2)

Widening of the sagittal suture and left lambdoid suture The left parietal bone was markedly displaced in relation to the parietal bone of the other side The occipital synchondrosis was widened bilaterally and the tip of the occipital bone was displaced inwards relative to the adjacent parts of the parietal bones

Pathological anatomical A large subgaleal hæmatoma and a rightsided cephalhæmatoma A 3 4 cm long rupture of the sagittal suture between the parietal bones was seen (Fig 3) This suggested rupture of the synchondrosis was verified by microscopic examination.

The child had a minor rupture of the tentorium on the right side with insignificant hæmatoma No gross signs of injury to the cerebral parenchyma or brain stem were seen



Fig 2 Case 1 Impression of tip of occipital bone and widening of sagittal suture X ray taken 4 hours after birth



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Comment

In this case the patient had marked uterine contractions, which resulted in remarkably rapid spontaneous termination of delivery On check examination of the measurements of the pelvis of the mother after delivery, it was found that the distal part of the pelvis was very narrow

Presentation of the child was normal About 5-10 minutes after birth the child became very pale and hypotonic A fluctuation at the back of the head was observed and an extracranial hæmatoma was strongly suspected Since the child showed signs of intracranial damage in the form of clonic and general convulsions, intracranial injury was believed to be the cause of the poor condition of the child Deep depressions of the occipital bone shown by X ray were considered to support this opinion

In view of the findings at autopsy, one might, however, suspect that the child had had severe cerebral anoxia because of anæmic shock and that the convulsions and the cerebral symptoms might have been secondary

This was the first case of this type observed and did not receive adequate therapy in time

Case II (92472/62)

Obstetric A 20-year old primigravida Full term After 16 hours of labour delivery was completed with VE extraction because of bregma presentation and OP position with poor progress of delivery despite marked uterine contractions The fœtal head was turned from the occipito-posterior to the occipito anterior position Extraction was difficult and required half an hour extraction time

Pædiatric Birth weight 3,800 gm At birth the child s condition was normal Owing to pallor and muscular hypotonia 5 hours later the child was transferred to the Department of Pædiatrics The child was then in a state of severe shock Blood transfusion were given, but within 10 hours of birth the child died from respiratory and circulatory failure

Skull X-ray (Bedside 1st day of life)

Both parietal bones were elevated about 5 mm above the plane of the frontal bone No difference in level was observed sagittally and no depression of the occipital bone

Pathologic anatomical Large subgaleal hæmatoma (Fig 4) Fractures without dislocation of parietal bones Careful examination of the portion around the midline revealed a roughness with fibrin deposits suggesting a source of bleeding from the parietal synchondrosis On microscopical examination of the sagittal suture close to the parietal fractures a horizontal rupture of the synchondrosis was discovered

Intracranially, there was a small rupture of the tentorium with slight hæmorrhage The internal organs were of anæmic appearance

Comment

In the present case a full term primipara had a remarkably intense labour After 16 hours VE extraction was done because delivery did not advance



F g 4 Case 2 S bgaleal hæmatoma cover ng practically the ent re crown of the skull like a th ck mat of clotted blood

VE-ext act on in comb nation w th ntense labour and an abnormal presen ta on in this case may have been too great a mechan cal stra n on the head of the fœtus and resulted n fracture of the par etal synchondros s The result was large subgaleal hæmorrhage

Case III (92870 62)

Obstetric A 19 year old prim gravida Full term Marked labour wh ch requ red sedat on After 20 hour s labour del very was terminated by low VE-extraction Lasted for 12 minutes Attempts to turn the head from occiput pos erior to occiput anter or pos tion fa led

Pæd atric B rth we ght 3 850 gm The child was flacc d and asphyxial after del very It recovered after a wh le Palpation suggested fluctuat on at the back of the head and subgaleal hæmatoma was suspected The ch ld was the efore immed ately transferred for pæd atric observat on S r e the hæma toma n the back of the head d d not appear to increa e and since the child showed no s gns of shock blood transfus on was not cons dered ind cated. The hæmoglobin fell to 14 gm. 00 ml and was regarded as a probable s gn of loss of blood

The ch ld was well when t left hosp tal and at re-exam nat on 3 months later no h ng rema kab e was found

Skull X ray (1st day of l fe)

3 mm d fference n level between the par etal bones with the one par etal bone depressed No defin te d fference in level between the occip tal and parietal bones No fracture l nes

Comment

In this case presentation was abnormal in a primipara with poorly advancing delivery despite marked labour VE extraction was therefore done This, together with severe labour in combination with narrowness of the pelvis (later confirmed by X ray) was probably the cause of the rupture of the synchondrosis between the parietal bones The roentgenologically demonstrable difference in level between the parietal bones of the child supports the assumption of rupture of the synchondrosis as the source of bleeding

Case IV (86209/62)

Obstetric A 35 year old gravida III, para I Delivery was initially normal as was the presentation of the child After 6 hour s labour the fœtal head was crowning at the outlet The mother was given anæsthesia but was seized by panic on inhalation and as the fœtal head presented the mother suddenly pressed her legs together Uterine contractions continued and the legs were forced apart to make delivery possible

Pædiatric Birth weight 3 360 gm Immediately after delivery an increasing fluctuation was found at the back of the child s head The general condition of the child was satisfactory Increasing pulse and respiratory frequency without definite signs of shock suggested loss of blood, and the child was given blood transfusion Pressure bandages were placed over the skull The child soon made a rapid clinical recovery Anæmia did not occur and at re-examination a month later, the child was found to be normal

Skull X ray (4 hours after birth)

Both parietal bones had a marked angulation without difference in level in the region of the sagittal suture The occipital bone showed a depression which was 6 mm below the adjacent parietal bones Control X ray 3 days after birth showed regression, but not complete normalization

Comment

In this case the patient was a full term multipara with previous normal delivery The delivery in question was also normal until the head was crowning, when the mother pressed her legs together These facts and extremely active uterine contractions probably resulted in compression of the fœtal head Soon after delivery a probable subgaleal hæmorrhage occurred

Skull X ray supports this diagnosis

Discussion

Our material consist of 2 fatal cases, a spontaneous delivery and a VE extraction Autopsy showed in both cases an interparietal rupture of the synchondrosis and a large subgaleal hæma

toma Of the other two cases delivery was spontaneous in one and completed by VE extraction in the other Judging from the clinical picture subgaleal hæmatoma was the main lesion in these cases, too

Both children survived

If the pressure or extraction forces during delivery are not properly balanced it may result in uneven pressure on the cranium with a large displacement and possibly fracture of the bone plates The interparietal synchondrosis may then also be endangered and in two of our cases a clear rupture of the synchondrosis was demonstrated

In this respect it might be mentioned that a similar case has been published by Felding and Hägerstrand (1961)

Lange (1961) in his VE material reported 4 dead children in which autopsy never showed rupture of the tentorium but subgaleal hæmatoma was given as the cause of death

While many authors have previously been inclined to regard the use of the extraction instrument as the only cause of post natal subgaleal hæmatomas one should, in view of the observations set forth above, also consider the primary relation between the fœtal head and the birth canal It might be a contributory cause of complicated delivery with consequent post natal subgaleal hæmatoma

Judging from the present study the following symptoms may be useful in establishing a correct diagnosis General symptoms are pallor and muscular hypotonia As a sign of shock the cardiac and respiratory frequency increase Later the child may have various cerebral symptoms A local symptom is diffuse increase in consistency in and under the scalp It might be interpreted as a local extracranial oedema due to coagulated subgaleal blood With increasing hæmorrhage a fluctuating hæmatoma develops usually in the back of the head These cases require special attention *immediately* after birth Symptoms of shock may occur without the child showing any other symptoms For reasons given above extracranial hæmorrhage may be difficult to discover and the loss of blood may be difficult to judge Careful control of the child's general condition colour of the skin pulse and respiration is necessary Blood should be at hand for transfusion in

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suspected subgaleal hæmatoma The hæmorrhage may increase the first days after delivery

With adequate therapy the prognosis can surely be improved Otherwise as shown by previous publications and our present series, the prognosis may be very poor *quoad vitam*

SUMMARY

Four cases of post-natal subgaleal hæmatoma are described, including two with a clear rupture of the interparietal synchondrosis and a fatal issue In the other two cases in which the children survived, clinical and roentgenological evidence suggested the same type of subgaleal bleeding In view of the present series in which two children were delivered spontaneously and 2 by VE extraction, the occurrence of subgaleal hæmatomas cannot always be ascribed to the use of the VE-instrument The observations made indicate that special care should be exercised on active turning of the fœtal head, especially in the event of disproportion between the head and the pelvic outlet

Children with subgaleal hæmatoma should be referred immediately for observation and active therapy

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RESULTS OF OPERATIONS FOR STRESS INCONTINENCE

A Study Based on Patients Operated on During the Years 1952—1960

BY

BENT COLLATZ CHRISTENSEN AND ERLING ØSTERGAARD

Introduction

In the present paper stress incontinence is taken to mean involuntary discharge of urine when the intra abdominal pressure suddenly increases e g on coughing

The pathogenesis of this condition is still a matter of dispute No doubt several ætiological factors may operate to varying degrees in each individual case for example, congenital traumatic and functional disorders of the female pelvis (Youssef 1960) In most cases stress incontinence is due to insufficiency of the involuntary internal urethral sphincter either because this muscle itself is weakened or overstretched or because its attachment in the region of the trigone and bladder neck has varied from normal disturbing the closing mechanism Often this occurs because the bladder neck has descended. In these instances the voluntary external urethral sphincter is not sufficiently strong to resist an acute increase in intra abdominal pressure

According to Enhorning (1961) the hydrostatic pressure in the bladder neck and the upper part of the urethra normally changes *pari passu* with that of the abdominal cavity An increase in abdominal pressure is counteracted by a simultaneous increase

in the pressure in the bladder neck region and the upper part of the urethra But if the urethra and bladder neck have descended to a point below and beyond this range, an increase in intra abdominal pressure often results in such a marked difference between the pressure inside the bladder and the pressure in the region of the bladder neck that the sphincter mechanism is rendered insufficient

In accordance with this theory, which is experimentally well founded, any treatment of the condition must aim at elevating and fixing the region of the bladder neck within the pressure range of the abdominal cavity

From the multitude of methods worked out for the operation of stress incontinence it is evident that the management of this disease is one of the most exacting tasks within gynæcological urological surgery The results depend to a great extent upon the selection of the materials and upon the technique, and no surgeon has been able to report 100 per cent good results The methods used may be divided into vaginal and abdominal methods and combinations thereof

Out of the vaginal methods there are simple procedures like the Kelly (1913), and Kennedy (1937) repairs These are usually combined with various prolapse operations with the object of elevating and supporting the bladder-neck region by a repair of the tissues of the vagina, bladder, and pubovesical ligament More complicated vaginal methods are based on the formation of muscle or fascial slings fixed to and elevating the region of the bladder neck, e g the Ingelman Sundberg pubococcygeal repair (Ingelman-Sundberg, 1946 1952) or the Aldridge fascial sling repair (Aldridge, 1942) The latter, however, is a combination of a vaginal and abdominal operation Among the abdominal methods there is reason to mention the Marshall, Marchetti and Kranz abdominal vesico-urethral suspension (Marshall, Marchetti and Kranz, 1949)

Other methods are based on principles other than elevation of the bladder-neck region, such as the Ingelman Sundberg urethra kink' operation (Ingelman Sundberg 1951)—lengthening the urethra and submitting it to compression by the bulbo cavernous muscles to substitute for the lacking function of the internal

sphincter In rare cases retropubic vesico-urethrolysis (Ingelman Sundberg 1949) or resection of the hypogastric plexus (Ingelman Sundberg, 1959) may be indicated, the latter being performed in cases where a hypertonic bladder is a contributory cause to stress incontinence

In mild cases of stress incontinence, usually combined with a varying degree of prolapse, the present authors have often used a modification of the Kelly Kennedy procedure In severe and recurrent cases of stress incontinence without major prolapse we have employed the Ingelman Sundberg pubococcygeal repair and in a few cases the Marshall Marchetti operation

Material

The series was selected from among 942 patients who under went operation for uterine prolapse during the period 1952–1960 Out of these patients a total of 114 i e 12 per cent, had stress incontinence as well Ninety one have been followed up The series contains a further 44 patients whose main diagnosis was

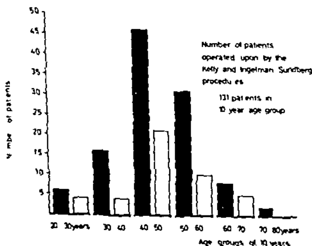


Fig 1 Number of patients in 10-year age groups treated by the Kelly operation (black columns) and the Ingelman-Sundberg operation (white columns) See text

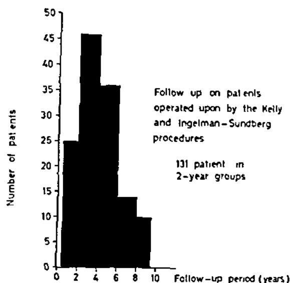


Fig 2 Number of patients in follow up periods of two years for 131 patients operated upon by the Kelly and Ingelman Sundberg procedures See text

stress incontinence and who had been submitted to the Ingel man-Sundberg pubococcygeal repair Out of this group 40 were followed up Thus, the present analysis comprises 91 patients treated by the Kelly-Kennedy operation and 40 treated by the Ingelman-Sundberg repair, a total of 131 treated by 149 opera tions

The age distribution is shown in Fig 1, which lists the total Kelly-Kennedy and Ingelman Sundberg series, and comprises 131 patients divided into 10-year age groups The youngest patient was 22 years of age and the oldest 77 The age distribution is approximately the same in both series, the majority of patients being in the age groups 40–60

The length of the follow-up period may be seen from Fig 2, in which the total series of 131 patients is given in 2 year groups The minimum follow-up period is 6 months and the maximum 9½ years More than half the patients had a follow up period between 2 and 6 years, and this applies to both the Kelly Kennedy and the Ingelman Sundberg groups

Other data of importance in relation to stress incontinence, such as body build and weight, parity, course of deliveries, oc currence of obesity, chronic bronchitis, bronchial asthma, were

not treated statistically, as the data were not sufficiently exact However, these problems will be mentioned in the discussion

Method of Investigation

In taking the histories a distinction was made between stress incontinence and other, more nervously conditioned disturbances, such as frequency and urgency of micturition Moreover, the patients were questioned regarding symptoms of prolapse and possible sexual difficulties after the operation

The physical examination included inspection of the vulva and vagina on straining and at rest Any prolapse and its degree was recorded The bladder was filled and its capacity was considered normal when it could hold 300 ml The patient was asked to strain and cough, first in the horizontal and then in the erect position

In mild degrees of stress incontinence there is dropwise dis charge of urine upon straining and coughing in the erect position but no stress incontinence in the horizontal position In more se vere cases there is dropwise or squirting discharge of urine on coughing in the horizontal as well as erect position

If the incontinence ceases upon elevation of the bladder neck region the indications for surgery and the surgical method to be adopted may be decided at the same time having regard to the factors mentioned in the discussion and conclusion Time con suming and unpleasant micturition urethrocystography was per formed only exceptionally and as a rule this is not necessary for evaluating the operative indication

Operative Technique

The Kelly Kennedy repairs used in the present series constitute a modification and extension of the original Kelly repair making up part of the Manchester operation An anterior vaginal repair is done isolating the cystocele which is invaginated by one or two purse string sutures The bladder ligaments are exposed and tied with 2-4 transverse mattress sutures (chromic catgut No 1) around the bladder neck and upper part of the urethra Redun

dant vaginal mucosa is resected and sutured with interrupted cat gut sutures The amputation of the cervix is performed by the method of Sturmdorff and the operation is finished by posterior colporrhaphy

The Ingelman-Sundberg pubococcygeal repair is performed as described by Ingelman-Sundberg An arcuate incision along the attachment of the anterior vaginal wall with dissection of the an terior vaginal wall right down to the anterior aspect of the cervix In this process it is necessary to cut ligamentous strands fixing the vagina in the corners of the operative field The bladder ligaments are now sufficiently exposed, and the pubococcygeal muscles are visible at the sides The bladder ligaments are united with a row of mattress sutures (chromic catgut No 1), elevating the region of the bladder neck well and solidly, the lowest sutures possibly including the anterior aspect of the cervix The pubococcygeal muscles are then exposed, cut as far posteriorly as possible, and swung in below the region of the bladder neck where they are united (chromic catgut No 2) The muscle sling is then fixed to the bladder ligaments to form one solid, firm musculo-fibrous support to the bladder-neck region The posterior ends of the pubococcygeal muscles are ligated and may be used in the sub-sequent posterior colporrhaphy Superfluous vaginal mucosa is resected, and the mucosa is stitched to the vulvar edge by inter rupted catgut sutures To obtain hæmostasis the procedure is finished by fairly firm gauze packing for 48 hours, and a Foley catheter is left in the bladder for 5 days

The Marshall-Marchetti Krantz operation is performed through a suprapubic incision giving access to the cave of Retzius, where the anterior aspect of the bladder and the urethra are freed of loose connective tissue and fat Thereafter, Ethicon 0 sutures are applied to both sides of the urethra and bladder neck region which are thereby elevated and fixed to the posterior aspect of the pubic bone and Cooper s ligament

In cases where surgery was contra-indicated because of poor general condition or senile atrophic mucosal changes and weaken ed muscles, we used conservative treatment consisting of active exercises of the pelvic floor and hormone therapy In the pelvic floor exercises the patient is instructed in contraction of the va

ginal and rectal orifices and drawing up the pelvic floor She is encouraged to carry out these active exercises at home in two or three series of 5–10 minutes daily Hormone therapy is administered topically in the form of an œstrone ointment or Dienœstrolum suppositories and systemically as oral œstrogens or parenteral androgens + œstrogens Conservative treatment was used also as a preoperative measure in cases where it was believed that the patients could be rendered more fit for operation

Results

According to the results of the clinical examination described above the patients were classified into the following 4 groups

Cured A Totally cured, i e cured of all micturition disturbances In order to be classified as cured the patient must not even have dropwise discharge of urine in the erect position at follow up On the other hand, a possible rectoenterocœle did not exclude a classification into group A

Cured B Cured of stress incontinence but other usually nervous micturition disturbances persist This includes cured patients in whom urgency or frequency of micturition persist or develop after the operation

The total of patients in groups A and B will hereafter be designated as cured

Improved Not a complete objective cure, but considerable improvement from the state prior to the operation The symptoms are so mild that the patient is not annoyed by them and refuses further treatment

Not improved Stress incontinence not abolished by the operation and still considerable In the absence of contra indications all these patients were offered re operation

Lastly the individual groups and the entire series were divided into primary and secondary operations Primary operation means that the result is recorded on the basis of only one operation for incontinence Secondary operation means that the result is recorded on the basis of 2 or more operations for incontinence

Table I gives the results of all 149 operations performed on 131 patients

Table I *Total Series Results of 149 Operations for Stress Incontinence*

Operative Procedure	Cured A	B	A + B	Improved	Not Improved	Total number of operations
primary *Kelly Kennedy*	38 (37 3)	19 (18 6)	57 (55 9)	19 (18 6)	26 (25 5)	102 (100)
secondary Kelly-Kennedy	4	1	5	0	2	7
total	42 (38 5)	20 (18 4)	62 (56 9)	19 (17 4)	28 (25 7)	109 (100)
primary Ingelman-Sundberg	8 (36 5)	12 (54 5)	20 (91)	1 (4 5)	1 (4 5)	22 (100)
secondary Ingelman-Sundberg	3	8	11	5	2	18
total	11 (27 5)	20 (50)	31 (77 5)	6 (15)	3 (7 5)	40 (100)
primary Kelly Kennedy and Ingelman-Sundberg	46 (36 1)	31 (25)	77 (61 2)	20 (17)	27 (21 8)	124 (100)
secondary	7 (28)	9 (36)	16 (64)	5 (20)	4 (16)	25 (100)
Kelly-Kennedy and Ingelman-Sundberg total	53 (35 6)	40 (26 8)	93 (62 4)	25 (16 8)	31 (20 8)	149 (100)

Cured A Cured of all micturition disturbances
Cured B Cured of stress incontinence but other micturition disturbances persist
Figures in brackets Percentages

A total of 109 Kelly-Kennedy procedures were carried out The majority, 102, were primary operations in connection with operation for utero-vaginal prolapse and cystocœle The per centage not improved was high (25 5) and 26 patients with severe stress incontinence coexisting with prolapse were not cured of their stress incontinence Out of the 26 primary failures, 18 have later been submitted to the Ingelman Sundberg pubo coccygeal repair

In 7 cases the Kelly Kennedy operation was used as the secondary procedure These were patients with fairly mild stress incontinence co-existing with a recurrence of uterine prolapse Five patients were cured of stress incontinence, while two remained incontinent after the prolapse had been cured

In the total Kelly Kennedy group the percentage of failures was high about three quarters of the operations resulting in cure or considerable improvement, while in about one quarter the stress incontinence persisted

Forty Ingelman Sundberg cases were followed up This procedure was used with approximately the same frequency as a primary and a secondary operation In all cases it was done for severe stress incontinence which was the main complaint, symptoms of uterine prolapse being absent or mild The results of the primary operation were good only one out of 22 operations having failed. Secondary operation was done on 18 patients whose prolapse had been cured or improved by a previous Kelly-Kennedy procedure while the stress incontinence persisted Sixteen were cured or improved by the Ingelman Sundberg operation while two did not obtain improvement.

In the Ingelman Sundberg series as a whole the results were good more than 9/10 of the operations leading to cure or improvement

For the sake of completeness Table I gives the total result of the operations both Kelly Kennedy and Ingelman Sundberg The results were poorer after primary than after secondary operation This is presumably due to a wrong choice of surgical method in the primary operation in a certain number of cases (*cf* also under Discussion)

The 31 operative failures from Table I are described in more detail below

The 26 failures of primary Kelly Kennedy operation were patients with severe stress incontinence who had not improved after the usual prolapse operation even though particular regard was given to the incontinence *i e* by supporting the region of the bladder neck by a row of mattress sutures in the paravesical tissue and bladder ligaments Eighteen of these 26 unimproved patients later had re-operation by the Ingelman Sundberg pro

Table II *Complications in 131 Patients Operated Upon for Stress Incontinence*

Local and Extragenital Complications		Operative Procedure Kelly Kennedy 91 Cases	Operative Procedure Ingelman Sundberg 40 Cases
Local complications			
	Secondary healing	7	1
	Hæmatoma	1	1
	Inflammation of hæmatoma	1	0
	Slight postoperative hæmorrh	5	0
	Serious postoperative hæmorrh	0	0
	Total	14	2
Extragenital complications			
	Urinary infection	3	3
	Phlebitis	2	0
	Pneumonia	1	2
	Embolism	0	1
	Deaths	0	0
	Total	6	6

bococcygeal procedure, with a good result in 16 Eight of the 26 unimproved patients are still being followed Seven have been found suitable for re-operation either by the Ingelman Sundberg or by the Marshall Marchetti procedure but the patients have refused the operation The remaining patient, who has atrophic mucosal changes in the vagina and weak levators has been advised conservative treatment by pelvic floor exercises and hormones

After the secondary Kelly-Kennedy operation two patients did not improve One has been offered re-operation but refused and has therefore—like the other patient—received conservative treatment by pelvic floor exercises and hormones

After the Ingelman Sundberg pubococcygeal procedure three patients have not improved Two have later been cured by the

Marshall Marchetti operation and one by the Schauta-Wertheim interposition operation for prolapse of the uterus

Thus out of a total of 131 patients submitted to one or more operations for stress incontinence 121 (92 4 per cent) were cured or improved, while 10 patients (7 6 per cent) are still being fol lowed as unimproved

Complications

For practical reasons the complications were calculated as the number of complications observed at the last of possibly several operations, i e at 91 Kelly Kennedy and 40 Ingelman Sundberg operations The results are shown in Table II There were no deaths or serious complications One major hæmatoma occurred in each group The total number of complications mainly in significant among the 91 Kelly Kennedy cases was 20 (22 per cent) and among the 40 Ingelman Sundberg cases 8 (20 per cent)

Discussion

The present study is retrospective Accordingly we lack cer ta n important data which we would have liked to have detailed more exactly

The grading of the urinary incontinence before the operation was not as accurate as at follow up the records usually being less instructive than the patients own statements at follow up

Sphincterometry, cystometry, and urethroscopy before and after the operation had been done in so few cases that the re sults were not included in the analysis Similarly, there were only a few micturition urethro-cystographies As stated by Fatah Youssef (1960) these investigations may yield information of importance to the choice of surgical method

The number and course of pregnancies + deliveries plays an im portant role in the development of stress incontinence It is well known that stress incontinence generally afflicts women who have borne children It is often noted for the first time in con nection with pregnancy or parturition or it has started at a later date usually around the menopause Two factors may be operative, partly the increasing laxness of the tissues with advancing age

and partly a certain hormonal insufficiency with a consequently reduced tonus and mucosal atrophy Prolonged labour, with the fœtal head pressing against the pelvic floor for a long time, stretching and lengthening the muscles of the pelvic floor, is with out doubt an important ætiological factor in stress incontinence

In the present series the number of deliveries is known, but their course is not accurately known

The occurrence of obesity, chronic bronchitis and bronchial asthma was not anlysed statistically, as the data regarding these important ætiological factors were regrettably too inaccurate

Nervous micturition complaints, urgency and frequency of micturition, were present in more than half the patients of the Ingelman-Sundberg series and in almost half the patients of the Kelly-Kennedy series, distributed nearly equally through the groups cured, improved, and not improved After the operation for stress incontinence the number of patients with nervous micturition disturbances was somewhat smaller than prior to the operation, as a number of patients cured of stress incontinence were also relieved of nervous micturition complaints On the other hand, a few patients in the groups with less favourable results from the stress incontinence operation (improved and not improved) developed nervous micturition complaints which had not been observed prior to the operation In all, two of 21 Ingelman-Sundberg patients and five of 43 Kelly-Kennedy patients with nervous micturition complaints were relieved of these symptoms simultaneously with the cure of their stress incontinence Thus, there is little difference between the Ingelman-Sundberg and the Kelly-Kennedy series in respect to the occurrence of nervous micturition complaints, and the operations for stress incontinence had in the present series little effect upon the nervous micturition camplaints

A direct comparison between the results of the Kelly Kennedy and the Ingelman Sundberg procedures is out of the question, as the materials were selected in different ways The Ingelman Sundberg operations were performed chiefly on the most severe cases of stress incontinence Nevertheless, the results of the Ingelman-Sundberg procedure in our hands were better than those of the Kelly-Kennedy operation

Any comparison of our results with the results of others must be done with the reserve that the various series are hardly alike in respect to composition severity of stress incontinence, and length of follow up As far as the latter is concerned, the follow up period should be a minimum of 6 months

By the Kelly Kennedy operation we obtained cure in 56 9 per cent and improvement in 17 4 per cent while 25 7 per cent were not improved Compared with Kelly s original results from 1913 and 1914 our results are less favourable and also poorer than Kennedy s original results (1937) This may be due in part to Kennedy s short follow up period when his paper was published Our results are similar to those reported by other authors (Counseller 1951, Ingelman Sundberg 1952, and Cullen and Welch 1961) According to all the cited authors the milder degrees of stress incontinence may be permanently cured by the Kelly Kennedy procedure, possibly combined with a prolapse operation while the more severe forms of stress incontinence frequently recur

By the Ingelman Sundberg operation we obtained the same good results as Ingelman Sundberg (1952), 77 5 per cent being cured 15 per cent improved and 7 5 per cent failures

The majority of unimproved cases in the present Kelly Kennedy series were patients who had severe stress incontinence in connection with prolapse and in whom the Kelly Kennedy procedure was performed as a natural supplement to a prolapse operation The operation was primarily directed against the prolapse and was not in all cases sufficiently effective against the stress incontinence

As stated above eighteen of these unimproved cases were later cured or improved by the Ingelman Sundberg procedure which gives a considerably more effective elevation and support to the region of the bladdder neck The remaining 10 patients who did not obtain improvement by the Kelly Kennedy operation are still being followed Eight have proved suitable for reoperation which has been offered to them while two have such weak and atrophic tissues in the vagina and pelvic floor that hormone therapy and training of the muscles are indicated.

Only three patients were not improved by the Ingelman

Sundberg procedure On the basis of the operative reports it is impossible to find out whether the tissues were inadequate or the surgical technique was faulty However, in two of these three patients the stress incontinence has later been cured or considerably improved by the Marshall Marchetti procedure and in one by the Schauta-Wertheim interposition operation for prolapse of the uterus

After completing the present follow up (in March 1961) we have performed 7 Ingelman Sundberg operations and 13 Marshall Marchetti operations on the above indications To date, all these patients are cured or improved

Conclusions

Our material and follow up have shown that stress incontinence commonly co-exists with uterovaginal prolapse In our series it was present in 12 per cent of 942 patients operated on for prolapse

The objective demonstration of the incontinence and its severity is important It may be performed by a simple standardized clinical investigation as used by us If the incontinence ceases upon elevation of the bladder-neck region, the indication for surgery and the surgical method may be decided at the same time Cumbersome and unpleasant micturition cystographies are seldom needed to supplement the investigation

On the basis of the experience gained from the present follow up, the authors feel that they can formulate certain indications for the use of the Kelly-Kennedy operation, the Ingelman Sundberg pubococcygeal repair, and the Marshall Marchetti operation

Depending upon the severity of symptoms and their coincidence the following schemes are proposed

1 *Prolapse combined with fairly mild stress incontinence* indicates the Manchester operation plus the Kelly Kennedy procedure
2 In patients with *severe stress incontinence with minor prolapse* the Ingelman Sundberg operation is preferable as the primary procedure This, however presupposes well de-

veloped pubococcygeal muscles and a reasonable vaginal access Otherwise the Marshall Marchetti operation should be performed

3 In patients with *severe prolap e with severe stress incontinence* the primary procedure should be the Manchester operation combined with a Kelly Kennedy procedure If the operation is carried out under local anæsthesia, the patient may be tested for continence as described above, and if she is still incontinent the procedure is supplemented by the Marshall-Marchetti operation

4 In patients with *recurrence of stress incontinence following the Manchester procedure and a simultaneous severe recurrence of the prolapse* the Kelly Kennedy procedure should be repeated combined with a re-operation for the prolapse

5 In patients with *recurrence following the Kelly Kennedy procedure and minor prolapse* the Ingelman Sundberg pubococcygeal repair is preferred Presuppositions and alternative procedure as stated under item (2)

6 In patients with *recurrence following the Ingelman Sundberg procedure* and in the presence of poor anatomical conditions (*cf* item 2) re operation by the method of Marshall Marchetti is preferred

7 *The Marshall Marchetti operation* is *preferred as a primary procedure* when there is a simultaneous indication for laparotomy especially if the stress incontinence is severe

As mentioned under operative procedures pelvic floor exercises and hormones topically or systemically are used partly in preparation of menopausal patients for operation and partly as the only treatment when operation is not accepted by the patient or contra indicated in poor risk cases

In our experience these relatively simple procedures used in the named sequence in cases of recurrence can cure or considerably improve practically all cases of stress incontinence which in the named clinical test are rendered continent by elevating the region of the bladder neck

SUMMARY

The ætiology and pathogenesis of stress incontinence are mentioned, emphasizing Enhorning's theory. After describing the method of examination and the operative technique, the results of 149 operations for stress incontinence on 131 patients are submitted. Out of 109 Kelly-Kennedy operations 3/4 were successful, while the results were not so favourable in the remaining 1/4. The Ingelman Sundberg operation gave a good result in more than 9/10. Out of three patients who were not cured by the Ingelman Sundberg procedure two were cured or improved by the Marshall-Marchetti operation and 1 by interposition of the uterus. Out of a total of 131 patients 121 were cured or improved by one or more operations, while 10 patients are still being followed. There were no deaths or serious complications. Finally, the results are discussed, and on the basis of the experience from the follow-up study conclusions are drawn regarding the ranges of indication for the Kelly-Kennedy, Ingelman Sundberg, and Marshall-Marchetti operations. By these simple procedures, used according to the given criteria, most patients with stress incontinence may be cured or considerably improved.

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SUBMUCOUS MYOMAS

BY

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The myoma is the most common tumour of the uterus, its absolute incidence (incidence of myomata from *post mortem* material) being about 19 per cent, and relative incidence (incidence of myomata from gynæcological patients) about 5 3 per cent with some variation in the different series published in the literature (Albrecht 1928 Essen Moller 1901, Fain 1935 Heynemann 1955, Krokfors 1960, Mayer, 1927, Mittelstrass 1955, Novak, 1958 Rubin, 1958 Sohnius 1934 v Peham 1931 Troell 1910)

A submucous myoma is a muscular tumour situated beneath the mucosa and adherent to the wall of the uterus with the greater part of the tumour bulging into the cavity (Albrecht Martius 1958 and Mittelstrass) Generally the submucous myoma is at first intramuscular but with increasing size it grows in the direction of least resistance towards the cavity (Albrecht Bjorkqvist 1911 Borner 1930 Mittelstrass) However myomas may be submucous from the onset and therefore it may be more accurate to speak of primary and secondary submucous myomas (Bjorkqvist, Meyer 1930 Mittelstrass) From the uterine wall a submucous myoma may continue its growth into the cavity and develop into a pedunculated submucous myoma A pedunculated submucous myoma may continue to grow towards the cervical canal and through the external os into the vagina This expansion into the vagina may be due

mainly to the concomitant action of three factors 1) growth of the myoma, 2) congestion of the myoma chiefly because of a disturbed blood circulation, and 3) uterine contractions, favouring expulsion (Amann, 1906, Bjorkqvist, Borner, Kitagawa, 1914)

Submucous myomas comprise, on the average, 19 7 per cent of all myomas, the incidence varying in the different reports in the range 2 4—30 7 per cent (Albrecht, Frankl, 1914, Jacobson, 1903, Krokfors, Sohnius, Terada, 1934, Trapp, 1939) Their incidence increase with parity (Kangas, 1935, Lynch, 1927, 1930) It has been suggested that during involution of the uterus an intramural myoma more readily becomes submucous (Lynch) Conversely, myomas in other situations decrease in number with parity (Krokfors and Kinnunen, 1962)

Myomas occur most commonly towards the end of the period of sexual maturity between 40 and 50 years of age, and they are very rarely encountered before the age of 20 years Submucous myomas develop still later, usually at the end of sexual maturity (Albrecht, Bjorkqvist, Jacobson, Kangas, Kitagawa, Krokfors, Mittelstrass, Morton 1958, v Peham, Sohnius, Terada, Trapp, Troell, Vara, 1949) With increasing parity myomas tend to appear later (Krokfors and Kinnunen, 1962)

Opinions differ concerning the time of the menarche in patients who later developed myomas In the opinion of Albrecht and Troell it occurs earlier, a view not shared by Essen Moller and Heynemann On the other hand the menopause is delayed in affected patients and menstruating period is therefore longer (Albrecht Heynemann Jacobson, Meyer, Morton, Sohnius Terada, Troell)

No definite correlation has been observed between the occurrence of myomas and the marital status of the patient, the information on this point being conflicting (Albrecht Mittelstrass, Sohnius, Troell)

The generally accepted opinion is that myomas decrease fertility, whilst no difference is observed in primary fertility but there is an increase in the incidence of secondary infertility, and

patients with myomas become infertile at an earlier age than other women The critical age is from about 26 to 29 years (Jacobson Harjola, 1949, Heynemann, Huber, 1939, Kitagawa, Mittelstrass, Trapp) Usually the infertility is not ascribable so much to the myoma itself as to the associated tubal endometriosis that causes occlusion of the Fallopian tubes (Huber, Philipp and Huber, 1939) The extent to which a submucous myoma causes infertility by being an obstruction to fertilization is a subject of varying opinion, but it is probable that it plays some part (Harjola Jacobson Kitagawa, Krokfors, Trapp)

Endometriosis is more common in association with myomas than normally (Albrecht, 1955, Vara)

Hyperplasia is the most common change in the endometrium (Bjorkqvist, Häggstrom, 1932 Lohmayer and Velten 1957 Morton Thiessen 1950 Torpin *et al* 1942 Zacharias 1954) However mechanical causes also play an important part and endometrial œdema may be confused with hyperplasia (Albrecht Frankl 1914 Meyer Mittelstrass Thiessen) The opposite condition—atrophy of the mucosa—may also be encountered (Mittelstrass) The submucous vasculature in the area of a submucous myoma consists of a dense network of veins with sinusoid dilatations running parallel with the surface The emptying of the veins is impaired resulting in persistent congestion in this area The impaired circulatory conditions distension and mechanical factors cause mucosal atrophy and hæmorrhage (Frankl) Pedunculated myomas may be pushed by the uterine contractions into the cervical canal and there become compressed Due to the resulting stasis a formation resembling the caput succedaneum seen during delivery develops in the myoma below the circle of contact and there is then a tendency to bleed (Pelkonen)

Various degenerative changes may occur in myomas The most common is necrosis which occurs in about 7—10 per cent of cases It is most frequently encountered in submucous myomas (Bjorkqvist Frankl Heynemann Jacobson Kervinen Lawrence *et al* 1956) Meyer Mittelstrass Novak Scipiades 1941 Sohnius v Peham)

Myomas may also undergo calcification, *mainly due to im paired blood circulation* and this change therefore occurs most often in necrotic myomas The calcification is frequently pre ceded by fibrotic or hyaline degeneration (Albrecht, Frankl, Jacobson, Heynemann, Kitagawa, Meyer, Mittel strass, Sohnius)

Fibrous, hyaline, fatty, mucous, amyloid changes, and cystic degeneration may also occur (Frankl, Heynemann, Kita gawa, Meyer, Mittelstrass, Novak, Sohnius)

Malignant degeneration is sometimes seen Sarcomatous trans *formation has been found in 0 5--4 per cent of cases* (Frankl, Jacobson, Mayer, Novak, v Peham, Sohnius) Car cinomatous myomas have also been encountered, though the in cidence is not higher than carcinoma of the uterine body How ever, the incidence of carcinoma in the myomatous uterus is higher than the mean incidence of uterine carcinoma (Al brecht, Meyer, v Peham, Sohnius)

Rarely a malignant tumour situated elsewhere in the body may metastasize into a myoma (Meyer)

A submucous myoma often becomes infected, especially if *necrotic The infecting organism may be any bacterium,* though tubercle bacilli are rarely encountered (Fain, Frankl, Hey nemann, Kitagawa, Levkova, 1959, Mittelstrass)

Rarely a submucous myoma causes inversion of the uterus Uterine contractions force the submucous myoma downward, which together with the weight of the tumour and abdominal pressure cause inversion This, however, will occur only if a part of the uterine wall is more or less atonic (Albrecht, Amann, Bjorkqvist, Engstrom, 1911, Jaschke, 1929, v Peham, Schauta, 1903, Turtola, 1949, Wallgren, 1900)

A submucous myoma has occasionally been found to become adherent to the wall of the uterus (Fink, 1930, Heynemann, Meyer, Szathmary, 1930) or of the vagina, if this is the site of origin (Amann) In such cases the myoma may produce atresia and hæmatometra (Meyer)

Uterine contractions may result in rupture of the uterus in very rare cases (Berutti and Volante, 1933, Gallerani, 1930, Heynemann) Torsion of a pedunculated submucous

myoma has also been encountered (Engstrom, Heynemann, Kitagawa)

Symptoms

Hæmorrhage, either meno- or metrorrhagia, is the most common symptom from a submucous myoma and may occur in as many as 85—90 per cent of cases The bleeding varies in degree and usually is more profuse with pedunculated myomas (Albrecht, Bjorkqvist, Frommolt, Heynemann, Jacobson, Kangas, Kervinen, Kitagawa, Morton, Pelkonen, Sohnius, Trapp, v Wachenfeldt) Anæmia is therefore encountered in about 33 per cent of patients with submucous myoma, whereas the incidence of anæmia is about 14—20 per cent in other patients with myomas (Bjorkqvist, Heynemann, Jacobson, Kangas, Kitagawa, Lawrence *et al* Morton, Sohnius) About 30 per cent of patients with submucous myoma have leukorrhœa, which frequently is blood stained discharge as a result of increased stasis, infection or necrosis (Bjorkqvist Heynemann, Jacobson, Kangas, Morton Sohnius)

Pain occurs in 20—40 per cent of patients It is usually relatively mild, but severe pain resembling labour pains occurs when a submucous myoma is expelled by the uterus through the cervical canal into the vagina

Patients with submucous myoma, especially of the pedunculated type may sometimes complain of dysmenorrhœic pain and painful coitus (Bjorkqvist Heynemann Jacobson, Kangas Kitagawa Sohnius v Peham Troell Wertheim 1904)

Painful defæcation is relatively rare, occurring in about 3 per cent and dysuria in about 20 per cent of cases The latter is more common in patients with a pedunculated submucous myoma that has been expelled into the vagina (Jacobson)

Treatment

The treatment of submucous myomas is surgical if the patient is a good operative risk The approach is vaginal or abdominal (Heynemann Kangas) Radiotherapy may be considered

in inoperable cases, but the results have been poor This treatment cannot be used on pedunculated submucous myomas (Heynemann, Kervinen)

Present Series

The present series consisted of all patients with myomas treated in the Second Department of Obstetrics and Gynæcology of the University Central Hospital, Helsinki, in 1945—1959

The patients with submucous myomas were divided into two groups, as follows

A Patients with a submucous myoma only,

B Patients having, in addition to a submucous myoma, one or more myomas in other situations (intramural and/or subserous) but with the submucous myoma dominant

A total of 3,771 patients with myomas were treated during this period Of these patients

Group A comprised 232 patients
" B " 309 "

Further data on this distribution is given in Table I The sites

Table I *Number of Cases*

	No of Patients	As Per Cent of All Myomas	As Per Cent of All Submucous Myomas
A	232	6 2	42 9
B	309	8 2	57 1
Total	541	14 4	—

of the wholly submucous myomas are shown in Table II

Table II *Sites of the Wholly Submucous Myomas*

	No of Patients	Per Cent
Vagina	41	17 7
Cervical canal	28	12 1
Uterine cavity and wall	163	70 2

The mean age of the patients was as follows

Group A	44 2 ± 0 41 years
„ B	44 5 ± 0 09 „
Total group	44 40 ± 0 24 years

The patients are grouped according to age in Table III

Table III *Patients Grouped According to Age*

Age	Group A		Group B		Total Series	
	No of Patients	Per Cent	No of Patients	Per Cent	No of Patients	Per Cent
Under 29	5	2 22	1	0 33	6	1 13
30—34	11	4 89	8	2 62	19	3 58
35—39	32	14 22	40	13 12	72	13 59
40—44	62	27 56	93	30 49	155	29 25
45—49	86	38 22	120	39 34	206	38 87
50—54	22	9 78	37	12 13	59	11 13
55—59	1	0 44	4	1 31	5	0 94
60—64	6	2 67	1	0 33	7	1 32
65—69	—	—	1	0 33	1	0 19
Total	225	100 00	305	100 00	530	100 00

The mean age at menarche was

Group A	14 4 ± 0 13 years
B	14 4 ± 0 12
Total group	14 4 ± 0 09 years

Duration of the menstrual flow before onset of the symptoms was

Group A	4 33 days
B	4 48
Total group	4 42 days

Menstruation was irregular in

Group A	10 cases = 5 6 per cent
B	19 = 8 3
Total series	29 cases = 7 5 per cent

A distribution of the parity of the patients by age is presented in Table IV

Table IV *Distribution of Parity of Patients by Age*

Parity	Group A		Group B		Total Series	
	No of Patients	Per Cent	No of Patients	Per Cent	No of Patients	Per Cent
Single 0	25	13 81	59	26 58	84	20 84
Married 0	24	13 26	46	20 72	70	17 37
I	38	21 00	44	19 82	82	20 35
II	38	21 00	31	13 97	69	17 12
III	29	16 02	30	13 51	59	14 64
IV	10	5 52	7	3 15	17	4 22
V	5	2 76	2	0 90	7	1 74
VI	5	2 76	3	1 35	8	1 98
VII	2	1 11	—	—	2	0 50
VIII	—	—	—	—	—	—
IX	1	0 55	—	—	1	0 25
X	4	2 21	—	—	4	0 99
Total	181	100 00	222	100 00	403	100 00

Tables V and VI show the nature and duration of the symptoms The erythrocyte sedimentation rate was regarded as elevated when it was above 12 mm/1 hr and anæmia was considered to be present in patients with a hæmoglobin level of less than 60 per cent

An X-ray hysterography of the uterus was made in

Group A	44	cases
„ B	43	„
Total series	87	cases

Table

	Menorrhagia		Metrorrhagia		Menorrh + metrorrh		Blood stained Discharge		Leukorrhœa		
	No		No	•	No		No		No		N
Group A	121	66 1	114	62 3	64	35 7	14	7 7	30	16 4	3
Group B	154	67 3	92	40 2	57	24 9	8	3 5	30	13 1	2
Total	275	66 6	206	50 0	121	29 4	22	5 3	60	14 6	5

Table VI *Duration of Symptoms*

Duration Years	Group A No of Patients	Group A Per Cent	Group B No of Patients	Group B Per Cent	Total Series No of Patients	Total Series Per Cent	
—½	45	28 66	46	25 27	91	26 84	
—1	39	24 84	45	24 73	84	24 78	
—2	38	24 21	42	23 08	80	23 60	
—3	17	10 83	25	13 73	42	12 39	
—4	6	3 82	12	6 59	18	5 31	
—5	2	1 27	3	1 65	5	1 48	
—6	5	3 19	4	2 20	9	2 65	5 60
—7	2	1 27	—	—	2	0 59	
—8	2	1 27	2	1 10	4	1 18	
—9	1	0 64	1	0 55	2	0 59	
—10	—	—	—	—	—	—	
Over 10	—	—	2	1 10	2	0 59	
Total	157	100 00	182	100 00	339	100 00	

and the result was doubtful in

Group A	8 cases	= 18 2 per cent
,, B	2 ,,	= 4 7 ,, ,,
Total series	10 cases	= 11 5 per cent

In all the other cases the X ray examination gave definite and accurate evidence

Endometriosis was encountered in

Group A	19 cases	= 8 2 per cent
B	52	= 16 8 ,, ,,
Total series	71 cases	= 13 1 per cent

[illegible] toms

Dysmenor-rhoea No	%	Other P [illegible] No	%	P [illegible] defecation No	%	Dysuria No	%	Elevated E. S. R. No	%	Anaemia No	%
33	18 0	81	44 3	6	3 3	15	8 2	124	58 8	89	41 8
53	23 1	104	45 4	13	5 7	31	13 5	147	52 5	73	26 1
86	[illegible]	185	44 9	19	4 6	46	11 2	271	55 2	162	32 9

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Single 0	25	13 81	59	26 58	84	20 84
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II	38	21 00	31	13 97	69	17 12
III	29	16 02	30	13 51	59	14 64
IV	10	5 52	7	3 15	17	4 22
V	5	2 76	2	0 90	7	1 74
VI	5	2 76	3	1 35	8	1 98
VII	2	1 11	—	—	2	0 50
VIII	—	—	—	—	—	—
IX	1	0 55	—	—	1	0 25
X	4	2 21	—	—	4	0 99
Total	181	100 00	222	100 00	403	100 00

Tables V and VI show the nature and duration of the symptoms The erythrocyte sedimentation rate was regarded as elevated when it was above 12 mm/1 hr and anæmia was considered to be present in patients with a hæmoglobin level of less than 60 per cent

An X-ray hysterography of the uterus was made in

Group A	44	cases
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Total series	87	cases

Table V N

	Menorrhagia		Metrorrhagia		Menorrh + metrorrh		Blood stained Discharge		Leukorrhœa		Labour Pain	
	No		No		No		No		No		No	
Group A	121	66 1	114	62 3	64	35 7	14	7 7	30	16 4	34	18 6
Group B	154	67 3	92	40 2	57	24 9	8	3 5	30	13 1	20	8 7
Total	275	66 6	206	50 0	121	29 4	22	5 3	60	14 6	54	13 1

ment other than curettage Details of the treatment in groups A and B are given in Table VIII Four cases (0 76 per cent) ended fatally The procedures in these are shown in Table IX

Table IX. *Mortality*

Number	Age Years	Operation	Cause of Death
1	29	Subtotal hysterectomy	Pulmonary embolism
2	50	Subtotal hysterectomy	Pulmonary embolism
3	52	Total hysterectomy and bilateral salpingoophorectomy	Cerebral embolism
4	41	Subtotal hysterectomy	Not stated in case report

Discussion

In the present series of patients with myoma 6 2 per cent were cases with submucous myoma only and 14 4 per cent were cases with a predominant submucous myoma and additional myomas in other situations These figures are similar to those reported in the literature, which range from 2 4 per cent to 30 7 per cent and average 19 7 per cent (Albrecht, Frankl, Jacobson, Krokfors, Sohnius, Terada, Trapp)

There is a marked change in the site of the purely submucous myomas since the study by Kangas in 1935 in that the incidence of pedunculated submucous myomas and especially of those expelled into the vagina has greatly decreased This probably is chiefly due to the patients now seeking treatment earlier and for milder symptoms than was the case three decades ago

The age range and distribution of the patients in the present series are similar to those in the literature (Albrecht Jacobson Kitagawa Krokfors Mittelstrass, Morton, v Peham Sohnius, Terada Trapp Troell, Vara) Submucous myomas occur in the latter years of sexual maturity, the mean age in the present series being 44 40 ± 0 24 years whereas they are rarely encountered in young patients

According to Vara (1943) the mean age at menarche of Finnish women is 14 977 ± 0 022 years The mean age of patients born at the same time in the present series was 14 4 ± 0 13 years

Histological examination was carried out in a total of 277 cases (group A 129 cases, group B 148 cases) Histological specimens were only taken from patients with macroscopic evidence of changes Malignant degeneration was found in 4 cases=0 7 per cent, the pathologist's diagnosis in all of these being leiomyosarcoma Further data is given in Table VII

Table VII *Degeneration of Myomas*

Degeneration of Myoma	Group A No of Patients	Group A Per Cent a)	Group A Per Cent b)	Group B No of Patients	Group B Per Cent a)	Group B Per Cent b)	Total Series No of Patients	Total Series Per Cent a)	Total Series Per Cent b)
Necrotic	31	24 1	13 4	30	20 9	9 7	61	22 0	11 2
Hyaline	2	1 5	0 9	1	0 7	0 3	3	1 1	0 6
Infected	7	5 4	3 0	1	0 7	0 3	8	2 9	1 5
Thrombosed	1	0 8	0 4	0	0	0	1	0 4	0 2
Myxomatous	1	0 8	0 4	0	0	0	1	0 4	0 2
Cystic	1	0 8	0 4	0	0	0	1	0 4	0 2
Calcification	0	0	0	2	1 3	0 6	2	0 7	0 4
Malignant	3	2 3	1 3	1	0 7	0 3	4	1 4	0 7

a) As per cent of histologically examined cases
b) As per cent of total series

Treatment

Whenever the patient s condition permitted, the treatment was operative The operation was performed by the abdominal route in 445 cases and by the vaginal route in 78 cases Radiotherapy was given in 6 cases, and in 2 cases the patient declined all treat-

Table VIII *Treatment of Patients*

	Abdominal Route						Vaginal Route				
	Excision of myoma	Enucleation of myoma	Subtotal hysterectomy	Total hysterectomy	Subtotal hysterectomy and bilat salpingoophorectomy	Total hysterectomy and b lateral salpingoophorectomy	Excision of myoma	Total hysterectomy	Total hysterectomy and b lateral salpingoophorectomy	Radiotherapy	Curettage
Group A	2	16	65	31	15	17	57	17	—	2	1
Group B	4	17	152	60	33	33	2	2	—	4	1
Total	6	33	217	91	48	50	59	19	—	6	2

Table X. *Analysis of Parity and Age by χ^2-Test*

Age	χ^2	f	p	
0–35 yrs	$\chi^2=6\ 284$	f=2	$0\ 02<p<0\ 05$	almost significant
36–40 yrs	$\chi^2=10\ 081$	f=4	$0\ 02<p<0\ 05$	almost significant
41–45 yrs	$\chi^2=11\ 78$	f=6	$0\ 05<p<0\ 01$	tendency
46–50 yrs	$\chi^2=18\ 088$	f=6	$0\ 001<p<0\ 01$	significant
over 51 yrs	$\chi^2=8\ 519$	f=6	$0\ 10<p$	not significant

The symptoms in the present series were similar to those reported in the literature and there were no marked differences in this respect.

In the present series, 26 8 per cent of patients sought treatment within 6 months and 51 6 per cent within one year of the onset of symptoms It is a noteworthy fact that nearly one half of the patients suffered from their symptoms for over one year before seeking treatment and nearly 6 per cent had symptoms for over 5 years

The forms and incidences of degeneration that the myomas underwent in the present series correspond to those described in the literature (Albrecht Bjorkqvist, Frankl, Heynemann, Jacobson Kervinen Kitagawa, Lawrence *et al* Meyer Mittelstrass, Novak Scipiades, Sohnius v Peham) Necrosis was a more frequent finding in the cases with submucous myoma alone than in cases where other myomas were present also (group A 13 4 per cent, group B 9 7 per cent) Malignant degeneration was encountered in 0 7 per cent of all cases of submucous myoma.

The treatment was surgical whenever possible The mortality was 0 76 per cent which is in agreement with data in the literature (Bardy Eklöf Slangus 1963 Vara)

in group A, 14 4 $\pm$ 0 12 years in group B, and 14 4 $\pm$ 0 09 years in the whole series Statistical analysis of these series by the t test gave the following result, where t is the T value and f the number of degrees

Group A	$t=4$ 14,	$f=11{,}584$
„ B	$t=4$ 48,	$f=11{,}617$
Total series	$t=5$ 45,	$f=11{,}797$

Accordingly, the difference in all the groups is statistically highly significant, and in patients with submucous myomas the menarche occurs at a younger age than in Vara's series of healthy women

The duration of the menses and menstrual irregularity before onset of other symptoms were similar to those in healthy women (Tietze, 1955)

Analysis of the parity by the χ^2 test, using as control the first control series of Krokfors (1960), showed that myomas do not influence the parity in young women up to the age of 35 years, but that with increasing age the parity is relatively lower than in other gynæcological patients A separate analysis of groups A and B gives a similar difference, which, however, is not as clear in group A

Thus it appears probable that submucous myomas cause secondary but not primary infertility On the basis of the present study it is not possible to state whether this is a result of the myoma as such, or of the associated tubal endometriosis

In view of the small size of group A and especially of the number of multiparæ, a definite view is not obtainable on the effect of parity on the number of submucous myomas However, it seems probable that it has no noteworthy influence and that the number of purely submucous myomas increases with increasing parity On the other hand, in group B and in the whole series the incidence of myomas was higher in nulliparae than in multiparæ, and accordingly the submucous myomas in these groups show the same parity trends as myomas in other areas of the uterine wall, as seen in Table X (Krokfors, Krokfors and Kinnunen)

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SUMMARY

The case records were examined of 541 patients with submucous myoma treated in the Second Department of Obstetrics and Gynæcology of the University Central Hospital, Helsinki, in 1945—1959 The submucous uterine myoma was purely submucous in 232 cases (42 9 per cent), other myomas were also present but the submucous type predominated in 309 cases (57 1 per cent)

Submucous myomas occur towards the end of the period of sexual maturity, the mean age being 44 40 ± 0 24 years

Patients with submucous myomas have an earlier menarche than healthy women, the statistical difference being highly significant.

A marked change has occurred in the location of purely sub mucous myomas as compared with earlier studies, the proportion of pedunculated submucous myomas, especially of those extend ing into the vagina, being greatly decreased

The degenerative changes present in submucous myomas in this series correspond to those reported in the literature Malignant degeneration was seen in 4 cases (0 7 per cent) Four pa tients (0 7 per cent) died during treatment.

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STRUMA OVARII

BY

USKO NIEMINEN CLAËS VON NUMERS AND OLOF WIDHOLM

It is not uncommon to find thyroid tissue in ovarian teratome but large amounts are rare (Smith, 1946) If thyroid tissue predominates in the ovarian tumour, the tumour is called struma ovarii According to Higuchi and Kate (1960), the incidence of such struma ovarii is about 0 3 per cent of all solid ovarian neoplasms

As far as is known Boettlin (1889) was the first to describe a benign ovarian teratoma that contained thyroid tissue, cases of struma ovarii were reported in the last century by von Kahlden (1895) and Gottschalk (1899) among others Smith (1946) collected from world literature a total of 152 cases of struma ovarii but later Brocq Rouvillous and Gauchez (1959) found a total of 233 cases in the literature Published reports are mostly concerned with individual cases, seldom have series exceeded 10 cases In Finland there have been descriptions of 7 cases in all five by Castren (1941) one by Bjorkenheim (1952) and one by Turunen (1957)

Ætiology

Von Kahlden and Gottschalk believed that the thyroid tissue present in the ovaries derived from the ovarian follicles Gottschalk observed malignant growth in a part of the tu

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teria In series reporting a high incidence, struma ovarii has been taken to include even such cases with a small amount of thyroid tissue

Ovarian tumours containing thyroid tissue have been found in patients of all ages, although the mean age is fairly high 42 years (Smith, 1946) The youngest patient reported was 6 years (Merttens, 1897), and the oldest 74 years (Heinsen, 1932)

The thyroid tissue is mostly found in only one of the ovaries In 21 cases (approximately 14 per cent) of the series collected by Smith (1946) a tumour was also found in the contralateral ovary though only 6 (4 per cent) of these contained thyroid tissue

The size of the tumour may vary considerably Masson and Mueller (1933) described a case in which the area of thyroid tissue was only 6 mm in diameter In Gottschalk s (1899) case, the tumour was approximately the size of a child s head

Rotton and Towell (1956) described a case of malignant struma ovarii and reported that 16 similar cases had up to that time been described in the literature Struma ovarii may produce metastases in different parts of the body According to Emge (1940), some 5-6 per cent of ovarian strumas produce metastatic lesions which are not always malignant. Morgen (1924) followed for a total of 18 ½ years a patient who had such a metastasis Werth (1928), Shapiro (1930) and Emge (1940) have described metastases of struma ovarii in the omentum and mesentery Proescher and Roddy (1910) published a report of a case in which a metastasis was found in the liver Woodruff and Markley (1957) reported a chest metastasis produced by struma ovarii and metastases may also be found in bones (Eerland 1936 Aschkanasy 1936 and Wynne McCartney and McClendon 1940) In the case reported by Aschkanasy the bone metastasis was the first sign of the disease and the symptoms of hyperthyroidism disappeared after the metastasis had been removed The chest metastasis described by Woodruff and Markley was not revealed until 5 years after the removal of the ovarian tumour Smith (1946) divides the metastases produced by struma ovarii into three main groups

mour he described and he therefore called the neoplasm "folliculoma malignum" Kretschmar (1901) described a case similar to Gottschalk's and assumed that the growth was composed of lymphatic vessel endothelium, that is to say, he considered the tumour an endothelioma Kretschmar (1904) later changed his mind and admitted that the tissue was thyroid tissue which had metastasized into the ovary from the thyroid gland.

Pick (1902) was probably the first to suggest that thyroid tissue in the ovary must be classified among the dermoids, in other words, it must be of teratoid character, and he called such a tumour 'teratoma strumoides thyreoidale ovarii Pick assumed that in such a tumour thyroid tissue proliferated while other tissues were destroyed

Bell (1905) believed that such a tumour resulted from degenerative changes in a pseudomucinous cystadenoma. Bauer (1914) concluded that the tumour was a form of cystadenoma, the thyroid tissue developing from downgrowth of the surface epithelium into the cystadenoma

Although thyroid tissue is sometimes seen in a pseudomucinous cystadenoma the theories described above do not completely elucidate the ætiology of struma ovarii Today, however, there is almost general agreement that a struma ovarii is composed of genuine thyroid tissue, and is usually seen in a unilateral ovarian teratoma

The following observations support the view that the thyroid tissue in the ovary is identical with thyroid gland tissue the tissue contains more iodine than does normal ovarian tissue (e g, Emge, 1940), the substance inside the follicles is similar to that in the thyroid gland and stains in the same way (e g, Smith 1946), the tissue shows pathological changes similar to those in the thyroid gland (e g, Gottschalk, 1899), and finally, symptoms suggestive of thyrotoxicosis have occasionally been noted in some cases (e g, Kleine, 1934 Aschkanasy 1936, and Emge, 1940)

Pathology

Marcus and Marcus (1961) *point out that the incidence* of struma ovarii depends on the diagnostic factors taken as cri

teria In series reporting a high incidence, struma ovarii has been taken to include even such cases with a small amount of thyroid tissue

Ovarian tumours containing thyroid tissue have been found in patients of all ages, although the mean age is fairly high, 42 years (Smith, 1946) The youngest patient reported was 6 years (Merttens, 1897), and the oldest 74 years (Heinsen, 1932)

The thyroid tissue is mostly found in only one of the ovaries In 21 cases (approximately 14 per cent) of the series collected by Smith (1946) a tumour was also found in the contralateral ovary, though only 6 (4 per cent) of these contained thyroid tissue

The size of the tumour may vary considerably Masson and Mueller (1933) described a case in which the area of thyroid tissue was only 6 mm in diameter In Gottschalks (1899) case the tumour was approximately the size of a childs head

Rotton and Towell (1956) described a case of malignant struma ovarii and reported that 16 similar cases had up to that time been described in the literature Struma ovarii may produce metastases in different parts of the body According to Emge (1940), some 5–6 per cent of ovarian strumas produce metastatic lesions which are not always malignant Morgen (1924) followed for a total of 18 ½ years a patient who had such a metastasis Werth (1928), Shapiro (1930) and Emge (1940) have described metastases of struma ovarii in the omentum and mesentery Proescher and Roddy (1910) published a report of a case in which a metastasis was found in the liver Woodruff and Markley (1957) reported a chest metastasis produced by struma ovarii, and metastases may also be found in bones (Eerland, 1936, Aschkanasy 1936 and Wynne McCartney and McClendon 1940) In the case reported by Aschkanasy the bone metastasis was the first sign of the disease and the symptoms of hyperthyroidism disappeared after the metastasis had been removed The chest metastasis described by Woodruff and Markley was not revealed until 5 years after the removal of the ovarian tumour Smith (1946) divides the metastases produced by struma ovarii into three main groups

(a) local implantation, (b) regional metastases to distant organs, and (c) blood borne *metastases to distant organs*

Turunen (1957) described a case of struma ovarii combined with ascites and hydrothorax Kawahara (1963) published a report on a similar case and states that he found 6 cases of this type in the literature (the case described by Turunen was not among them) In the series compiled by Smith ascites occurred in 26 cases (17 per cent) and adhesions in 5 cases

Histology

Descriptions by various authors indicate that ovarian tumours containing thyroid tissue vary in appearance depending on the tumour's size and type Transverse section often reveals cavities of different size containing clear, thin fluid.

The histological structure of thyroid tissue seen in the ovary is similar to that of normal thyroid gland tissue, containing follicles coated by epithelium and filled with colloid (Morgen 1924, Smith, 1946) The follicles are round in shape, and the epithelium covering them is cuboidal or flattened. The colloid is *homogeneous, but locally vacuolated. The staining characteristics* are those of colloid and not mucin or pseudomucin The stroma is usually scanty The tumour tissue sometimes contains colloid filled dilated follicles and hyperplastic glands with small cavities This can be considered an indication of physiological activity at different levels (Smith, 1946)

There are a few reports of cases in which adenomatous proliferation (Plaut, 1933, MacGarrity and Dodson, 1948, Woodruff and Markley, 1957), papillary tumours (Manasse, 1926, Morgen, 1924), and adenocarcinoma (Moench, 1929, Wynne, McCartney and McClendon, 1940) have been noted

According to most recent reports, 5–10 per cent of ovarian strumas are *malignant (Marcus and Marcus 1961)* It is often difficult to diagnose malignancy since the demarcation line between a benign and a malignant process is vague, and the diagnostic criteria for malignancy are not uniform In Smith's opinion the assessment of malignancy is made particularly dif

ficult by the fact that thyroid tissue has no basement membrane between the glandular epithelium and the stroma Graham (1925) and Smith (1946) suggest that the invasion of blood vessels by thyroid tissue is the only reliable sign of malignancy

According to Smith (1946), ovarian tumours containing thyroid tissue can be divided into three main groups (a) dermoids containing thyroid tissue (about half of all cases), (b) cystadenomas containing thyroid tissue (about one-third of all cases) and (c) tumours containing thyroid tissue alone (about one sixth of all cases)

In addition to thyroid tissue, fragments of bone and cartilage have also been found in these tumours Their presence is not always a sign of teratoma for it is known that bone and cartilage may develop in different organs without any teratomatous growth (Marcus and Marcus, 1961) Nor is the occurrence of psammoma bodies uncommon

Symptomatology

Ovarian tumours are not usually diagnosed until, by their growth, they begin to produce discomfort for mechanical reasons such as pressure and torsion Like other ovarian tumours, those containing thyroid tissue seldom produce any general symptoms The diagnosis of struma ovarii is generally verifiable only by microscopic study (Marcus and Marcus 1961)

Authors have shown special interest in the occurrence of symptoms of thyrotoxicosis in connection with struma ovarii Reports on such cases have been published e g by Kovacs (1924) Kleine (1934) Aschkanasy (1936) Emge (1940) and Smith (1946) According to Anderson (1957) about 12 per cent of ovarian strumas are functional but thyrotoxicosis is very seldom evident According to the latest estimates the incidence of thyrotoxicosis is roughly 5-6 per cent (Marcus and Marcus 1961) Moench (1929) and McGarrity and Dodson (1945) described cases in which it was only after the tumour had been removed that the patient was found to have suffered from thyrotoxicosis and that the symptoms had disappeared The removal of struma ovarii may provoke an enlargement of the

thyroid gland (Foulkes and Fraser, 1954, Woodruff and Markley, 1957) or an outbreak of thyrotoxicosis (Trapl, 1912) In the series compiled by Smith (1946), the incidence of cervical goitre was 16 per cent

Present series

Between 1951 and 1962 the laboratory of the I and II Clinics of Obstetrics and Gynæcology, Helsinki University Central Hospital, received a total of 19 histological specimens from which struma ovarii could be diagnosed No diagnosis of struma ovarii was made unless the specimen contained plenty of thyroid tissue Of the 19 patients concerned, 6 were treated in the I and II Clinics of Obstetrics and Gynæcology at Helsinki University Central Hospital, while the remaining 13 were treated in hospitals elsewhere in the country Supplementary information on the patients was obtained from the attending doctors and the patients themselves

The histological specimens were fixed in 10 per cent formalin for 1–3 days and cut by microtoms into sections 5–6μ thick The sections were stained by the Hæmatoxylin- van Gieson and eosin methode All the specimens were examined by Professor Claës von Numers

Case 1

Unmarried woman aged 47 Menarche at the age of 14 Menstruation had always been scant and painful Nulliparous no abortions Perspiration had been unusually heavy for several years and from childhood the patient's eyes had been exophthalmic Two years previously a tumour had been noted in the right ovary it was considered benign and surgery was not hurried A few weeks prior to operation the patient had felt pain in the lower abdomen – Her sister had x ray therapy for thyrotoxicosis

At operation a tumour the diameter of 10 cm was found in the right ovary and another the diameter of 3 cm in the left ovary The uterus and both ovaries were removed.

Histological diagnosis Endometriosis of the right ovary Dermoid cyst of the left ovary (struma ovarii) The specimen taken from the left ovary arose from a cyst like ovarian tumour Its interior surface was lined partly by squamous epithelium partly by stratified columnar epithelium Stroma composed of connective tissue contained profuse thyroid tissue The tumour was benign

Post-operatively the patient's general pre-operative symptoms persisted in the same form with in addition occasional tachycardia No specific laboratory tests were made

Case 2

Married woman, aged 42 Menarche at the age of 14 Menstruation regular, of ordinary volume Para 2 one abortion Prior to the operation the patient had had backache for about 3 months For this reason she had consulted a doctor who noted a tumour in the right ovary and a 3 month pregnancy

At operation it was found that the uterus was roughly the size of a woman's fist that a tumour the diameter of 8 cm was situated in the right ovary but that the left ovary was normal. The ovarian tumour contained bloodstained liquid and its interior surface showed papillary growth somewhat suspicious of malignancy

Histological diagnosis Decidual reaction of the endometrium. Pregnancy Struma ovarii on the right side The microscopic sample of the ovarian tumour showed a small part of the wall to be cyst like in formation with hyalinized and partly calcified connective tissue The biopsy specimen was mainly composed of tumour tissue exactly similar in structure to thyroid tissue follicles of somewhat varying shape and size contained well stained colloid In several places structural features suggestive of hormonal activity were noticeable No proliferation that would suggest malignancy

After the operation, the serum protein bound iodine was 6 8 mg %, B M R +21 per cent the thyroid gland was of normal size and soft. The reactions of the pupils were normal lidretraction was considerable Graefe's sign was + and there was a slight tremor of the fingers The patient's palms were damp but the humidity of the skin was otherwise normal The patient had tachycardia (102 per min) her ECG was normal blood pressure 130/70 mm/Hg According to the internist the patient did not at least post operatively have thyrotoxicosis requiring treatment despite the slight symptoms suggestive of it[1]

Case 3

Married woman aged 29 Menarche at the age of 15 Menstruation regular but scanty Para 3 no abortions The patient had suffered from lung tuberculosis 10 years prior to the operation During this illness a tumour had been found in the right ovary but it had subsequently disappeared. Two years pre-operatively a tumour was discovered in the left ovary but gave no pain One month before the operation the patient cousulted a doctor for slight abdominal pain and a tumour was found in each ovary

At operation it was noted that the abdominal cavity contained some serous liquid The uterus was of ordinary size The right ovary contained a tumour approximately the diameter of 10 cm and the left ovary a mobile tumour which was roughly the diameter of 6 cm Both tumours were removed On examination the tumour from the right ovary was found to have a cavity

containing yellow serous fluid, the tumour wall was thick and jelly like, with out papillae Inside the tumour there was a smaller cavity containing sebaceous material and a small area with tiny cavities containing serous liquid. The tumour removed from the left ovary consisted of two separate cavities the larger containing sebum and hair, the smaller cavities filled with serous liquid

Histological diagnosis Dermoid cyst of the left ovary Dermoid cyst of the right ovary (struma ovarii) A microscopic specimen taken from the left ovary showed keratin forming squamous epithelium lining the interior surface of the cyst like ovarian tumour The wall showed large numbers of sebaceous and sweat glands There was no malignant proliferation. The microscopic specimen taken from the right ovary revealed a tumour which was partly cystic, and the interior surface of which was without epithelium It showed granulation tissue, with fragments of hair The bulk of the specimen consisted of thyroid tissue of varying degrees of differentiation, partly adenomatous There was no suggestion of malignancy

Post operative examination showed a smooth, rather soft node, approximately the size of a plum, in the patient s thyroid gland She showed no clinical symptoms suggestive of thyrotoxicosis

Hormonal analysis results gonadotropic hormones over 40 H U, oestrogenic hormones less than 50 H U, 17-ketosteroids 6 mg pregnandiol 0.4 mg

Case 4

Unmarried woman aged 46 Menarche at the age of 13 Menstruation regular and painful, ordinary in volume Nulliparous no abortions Two years before the operation the patient had had an apoplectic stroke with the left half of the body paralysed She had recovered almost completely In connection with the apoplexia hypertension and a slight cardiac defect had been noted About a year before the operation the patient s voice had grown deeper; examination by an otologist showed the vocal chords to be normal Three months pre-operatively a tumour roughly the diameter of 10 cm was found on the right side of the uterus

Operation revealed a smooth surfaced tumour the diameter of 12 cm growing from the left ovary The right ovary was normal A study of the tumour revealed that it contained teeth, sebum and hair

Histological diagnosis Dermoid cyst of the left ovary Struma ovarii A microscopic sample of the tumour revealed that the sections consisted of moderately differentiated thyroid tissue surrounded by fibrous connective tissue of ordinary structure No other tissues were seen in the sample

Post-operatively the patient s serum protein bound iodine was 6.0 mg % serum cholesterol 273 mg % The blood pressure was 210 100 mm Hg No symptoms suggestive of thyrotoxicosis were noted

Prior to the operation the patient had been subjected to hormonal analysis Results I in Table I The patient was subsequently given 100 mg of Cortison

Acetate on three days after which a second hormone analysis was performed Results II in Table I A third hormone analysis was performed after the operation, Results III in Table I

Table I *The results of the three hormonal anlyses (Case 4)*

		Analysis I	Analysis II	Analysis III
Œstrogenic horm		500 H U	450 H U	50 H U
17 KS		12 3 mg	12 8 mg	4 8 mg
17 OHCS		21 7 mg	26 7 mg	7 3 mg
17 KS fractions	U	1 5 mg (12 2 %)	1 0 mg (7 8 %)	0 2 mg (4 2 %)
	DHA	2 0 mg (16 3 %)	1 7 mg (13 3 %)	0 9 mg (18 8 %)
	A	41 0 mg (33 3 %)	2 8 mg (21 9 %)	1 4 mg (29 2 %)
	E	3 5 mg (28 4 %)	3 0 mg (23 4 %)	1 6 mg (33 3 %)
	Rest	1 2 mg (9 8 %)	4 3 mg (33 6 %)	0 7 mg (14 5 %)
Dehydroepiandrosterone		– –	0 2 mg (1 5 %)	0 4 mg (9 2 %)

The patient had received no hormone therapy of any kind before the operation She tended to lose hair There were no signs of masculinization of the body

Case 5

Married woman aged 43 Menarche at the age of 14 Menstruation regular normal in volume Para 1 no abortions Ten years prior to the operation the patient had undergone laparotomy no pathological changes had been noted in the genitale Six months pre operatively the patient started to menstruate irregularly and bled profusely Before the operation a tumour was observed behind the uterus

On operation it was found that the right ovary was covered with adhesions and showed a tumour approximately the diameter of 8 cm The left ovary showed a solid nodular tumour the diameter of 3 cm while the uterus contained a myoma the diameter of 5 cm

Histological diagnosis Dermoid cyst of the right ovary Struma ovarii on the left sid Leiomyoma of the uterus A microscopic sample taken from the right ovary showed a keratin producing squamous epithelium lining the interior surface of the cyst like ovarian tumour The wall composed of connective tissue showed numerous sebaceous glands There was no suggestion of malignancy The sample taken from the left ovarian tumour consisted throughout of moderately well differentiated thyroid tissue The tumour was partly surrounded by thick and greatly hyalinized connective tissue which showed patches of calcification There was no mal gnant proliferation

The patient showed no clinical signs of thyrotoxicosis Serum protein bound iodine 8 3 mg % and serum cholesterol 245 mg %

Case 6

Unmarried woman, aged 61 Menarche at the age of 16, menopause at the age of 50 Nulliparous no abortions For seven years prior to the operation the patient had felt pain suggestive of angina pectoris For some two months before the operation she had been conscious of constriction of the abdomen, flatulence and swelling An internal specialist was consulted pre operatively, whose findings were blood pressure 150/80 and universal arteriosclerosis Serum protein bound iodine 8 2 mg %, serum cholesterol 292 mg % Gynæcological examination revealed a tumour approximately the diameter of 12 cm on the left side of the uterus

At operation it was seen that the left ovary had a smooth surfaced, solid tumour, the diameter of 12 cm, embedded at the bottom of Douglas pouch The right ovary was normal The tumour was found to contain yellow, tallow like fluid and a knot of hair roughly the diameter of 3 cm

Histological diagnosis Dermoid cyst of the left ovary Struma ovarii A microscopic specimen taken from the tumour showed a total absence of epithelium of the interior surface of the cystic wall The wall was covered by a layer of granulation tissue of varying depth, with very many giant cells of foreign body cell type The wall of the cyst was composed largely of connective tissue There was one fairly extensive area composed of typical thyroid tissue, and near it a strip of nerve tissue of primitive structure There were no signs of malignancy

At the follow up examination the patient was well, though the cardiac discomfort persisted

Case 7

Unmarried woman, aged 46 Menarche at the age of 14 Menstruation regular, normal in volume Nulliparous, no abortions Pre operatively, the patient showed no symptoms suggestive of thyrotoxicosis For some time before the operation she had pain in the lower back and gynæcological examination revealed myomata in the uterus

At operation the left ovary was found to contain a tumour about the diameter of 12 cm, multilocular and containing clear liquid The right ovary was normal, and there were fibroids in the uterus

Histological diagnosis Adult ovarian teratoma Struma ovarii Uterine myoma A microscopic sample from the tumour showed that the biopsy specimens were composed of relatively acellular fibrous connective tissue, with occasional small ducts of columnar epithelium varying somewhat in quality and structure The bulk of the specimen consisted of fairly well differentiated tissue present as islets of varying size in a connective tissue matrix In structure it resembled thyroid tissue, with occasional features suggestive of endocrine function There was no suggestion of malignant proliferation

Case 8

Married woman aged 41 Menarche at the age of 13 Menstruation varying in volume slightly irregular Para 3 no abortions For a lengthy period prior to the operation the patient had suffered from headache and backache sometimes from nervousness She had felt pain in the left lower abdomen, and had consulted the doctor for this

At operation a cyst the diameter of 5 cm was found in the left ovary It contained a rather firm papillary area about 1 cm in diameter The right ovary was cystic but showed no papillae

Histological diagnosis Struma ovarii on the left side Corpus luteum in the right ovary A microscopic sample from the left ovary howed ovarian tissue in direct connection with tumour tissue which consisted solely of well-differentiated thyroid tissue The cyst was presumably a dermoid cyst The walls of the specimen however showed nothing more than the thyroid tissue mentioned There was no malignant proliferation

At a follow up examination the patient s nervousness and pain had disappeared completely

Case 9

Married woman aged 58 Menarche at the age of 15 Menstruation regular ordinary in volume Menopause at the age of 54 Para 4 no abortions Prior to the operation the patient had lost weight had been nervous and had felt a constructing pain in her chest The patient had consulted the doctor primarily for pain in the upper abdomen

At operation the left ovary was found to contain a cyst the diameter of 20 cm filled with clear liquid Its lower part showed a firmer area the size of an egg composed of numerous small cyst like cavities The wall of the cyst was smooth throughout. The right ovary was normal

Histological diagnosis Dermoid cyst of the left ovary Struma ovarii A microscopic sample from the tumour showed that the wall of the cyst like tumour was composed of hyalinized partly necrotic connective tissue extremely poor in cells and partly netlike in structure The inner surface lacked epithelium A part of the specimen consisted of well-differentiated thyroid tissue There were no signs of malignancy

At a follow up examination the patient s discomfort had disappeared She felt no more thoracic pain and was no longer nervous

Case 10

Unmarried woman aged 53 Menarche at the age of 13 Menstruation regular but scanty Menopause at the age of 52 The patient had generally been well shortly before the operation she had felt pressure in the lower abdomen

At operation the left ovary was found to contain a smooth-surfaced tumour the diameter of 12 cm The right ovary was normal



Fig 1 Partly well differentiated thyroid tissue partly areas corresponding to thyroid adenoma of foetal type



Fig. 2. Thyroid tissue with varying predominantly adenoma-like structure.
Case 1. Haem. van Gieson × 7



Fig 1 Partly well differentiated thyroid tissue partly areas corresponding to thyroid adenoma of foetal type

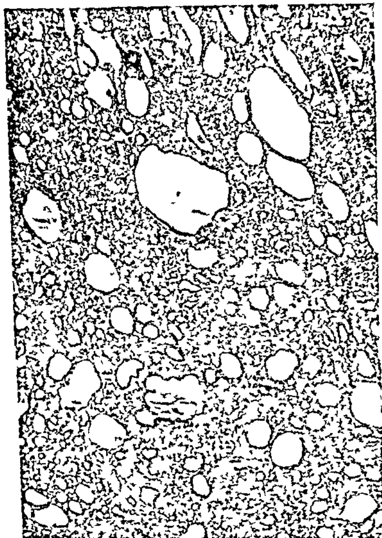


Fig 2 Thyroid tissue with varying predominantly adenoma like structure Case 10 Haem – van Gieson × 70

Histological diagnosis Dermoid cyst of the left ovary The microscopic sample taken from the tumour showed that the inner surface of the cyst was lined with keratin producing squamous epithelium The wall showed numerous sebaceous glands and very considerable areas made up of thyroid tissue of varying degrees of differentiation In the areas of greatest differentiation the follicular epithelium and colloid showed occasional slight changes suggestive of endocrine function (Figs 1 and 2)

The patient showed no symptoms suggestive of thyrotoxicosis either before or after the operation

Case 11

Unmarried woman, aged 38 Menarche at the age of 15 Menstruation scant and painful Nulliparous, no abortions Seven years before the operation the patient had undergone thyroidectomy for thyrotoxicosis Her habitus was asthenic, and symptoms suggestive of thyrotoxicosis had occurred even after thyroid ectomy Gynæcological examination revealed a right ovarian tumour No laboratory tests were made

At operation it was seen that the uterus contained fibroids the right ovary a smooth surfaced, light-coloured cyst the size of a fist, while the left ovary was normal

Histological diagnosis Struma ovarii on the right side Fibromyoma The microscopic sample from the cyst showed that the tumour was of teratoid character, composed of fibrous connective tissue in which islets of thyroid tissue occurred The thyroid tissue consisted of follicles containing large quantities of colloid, and locally showed features such as resorption vacuoles in the colloid, indicating endocrine function There was no malignant proliferation

After the operation the patient felt well for about five years, until commencement of climacteric symptoms

Case 12

Married woman, aged 39 Menarche at the age of 15 Menstruation regular, normal in volume Para 9 2 abortions Prior to the operation the patient had showed no symptoms properly suggestive of thyrotoxicosis but she had had dyspnœa and pain in the chest A month before the operation a tumour to the right of the uterus was diagnosed

At operation the right ovary was found to contain a twisted cyst the diameter of 15 cm containing brown liquid in which floated two tufts of hair and lumps of fat The left ovary was normal

Histological diagnosis Teratoma of the ovary hydatid of Morgagni The microscopic sample from the tumour showed stroma containing connective tissue and epithelial tissue of varying types On the surface there occurred stratified ciliated epithelium similar to that present in trachea The cavities were of varying size surrounded by connective tissue and contained numerous small follicular cysts of unstratified columnar or cuboidal epithelium

the cysts were filled with colloid substance This tissue looked very similar to thyroid tissue even though its epithelium was more diversified than that of normal thyroid tissue In places, the epithelium was fairly markedly proliferating though not malignant

No information is available on the patient s health since the operation

Case 13

Unmarried woman aged 48 Menarche at the age of 15 Menstruation irregular and profuse Nulliparous no abortions Prior to the operation the patient had no symptoms suggestive of thyrotoxicosis The thyroid gland was normal A dermoid cyst had been removed from the patient s right ovary 21 years prior to the present operation The patient had consulted the doctor for irregular menstruation and on this occasion a tumour was found left of the uterus

At operation a cyst the diameter of 8 cm was found in the left ovary the cyst was multilocular and had a light-coloured surface The right ovary had been removed.

Histological diagnosis Struma ovarii on the left side Cystic glandular hyperplasia of endometrium The microscopic sample from the tumour consisted of tumour tissue similar in structure to thyroid tissue throughout There were numerous follicles of cuboidal epithelium varying in shape and size mostly containing considerable quantities of colloid Between the follicles there was stroma composed of hyaline connective tis ue There were faint signs of endocrine function but no malignant proliferation (Fig 3)

No information has been obtained on the patient s health since the operation

Case 14

Married woman aged 46 Menarche at the age of 14 Menstruation regular normal in volume Para 2 one abortion and one ectopic pregnancy Prior to the operation the patient had had no symptoms suggestive of thyrotoxicosis She had consulted the doctor because of pain in the lower abdomen which she had felt over a number of years

The operation revealed a bilocular cyst the diameter of 12 cm in the left ovary One of the loculi was about the diameter of 5 cm and contained a yellowish decomposing mass while the other a bigger one contained yellowish serous liquid The right ovary was normal

Histological diagnosis Struma ovarii on the left side The microscopic sample revealed that the tumour was surrounded by a thin capsule of connective tissue The tumour itself was composed of dense and *very numerous* follicles surrounded by columnar or cuboidal epithelium the follicles were filled with colloid No signs of malignancy were visible

Since the operation the patient has been symptom free apart from slight menstrual disorders

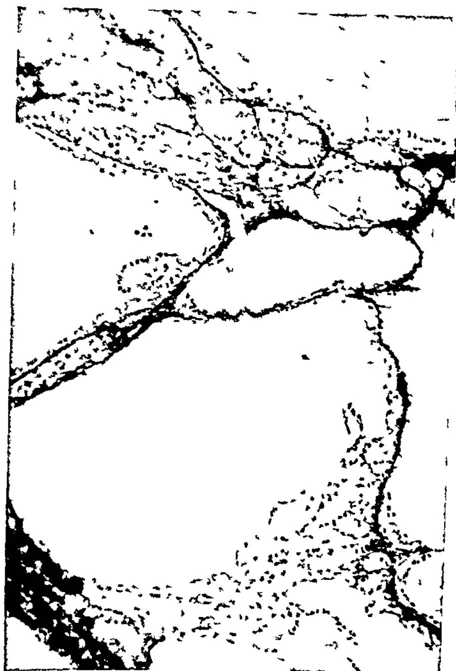


Fig 3 Thyroid tissue with follicles of varying size The structure of the epithelium and the vacuolated colloid indicate endocrine activity Case 13 Haem – van Gieson × 1 0

Case 15

Married woman aged 26 Menarche at the age of 14 Menstruation regular normal in volume Para 4 no abortions Prior to the operation the patient had no symptoms suggestive of thyrotoxicosis The thyroid gland was normal The patient had for some time felt pain in the lower abdomen

At operation a tumour the diameter of 12 cm was seen to grow from the right ovary When the tumour was split it was found to contain a large number of follicles filled with serous liquid The right ovary was normal

Histological diagnosis Struma ovarii on the right side The microscopic sample of the tumour consisted of tumour tissue locally adjacent to ovarian tissue of normal structure The tumour was composed of thyroid tissue throughout. This was partly well-differentiated largely similar to ordinary thyroid tissue partly less markedly differentiated in these latter parts the structure was that of the so-called fœtal thyroid adenoma In many places the tumour tissue formed smaller cysts which were filled with colloid There was no malignant proliferation

No information has been obtained on the patient s condition since the operation

Case 16

Married woman aged 43 Menarche at the age of 15 Menstruation regular, ordinary in volume Para 2 Prior to the operation the patient had experienced painful urination and her menstruation increased in volume

At operation it was found that a spherical tumour roughly the diameter of 6 cm emerged from the left ovary the sectional surface of the tumour consisted of several cavities containing serous liquid The right ovary was normal

Histological diagnosis Struma ovarii on the left side The microscopic study of a biopsy specimen of the tumour showed that the specimen consisted of a relatively thick walled ovarian cyst The wall consisted of fibrous connective tissue with many areas varying in extent of thyroid tissue and numerous follicles of varying size filled with colloid The interior surface of the cyst was lined with low cuboidal epithelium No signs of malignancy

Since the operation the patient has been well

Case 17

Married woman aged 47 Menarche at the age of 15 Menstruation normal in volume and regular Nulliparous no abortions For some years prior to the operation the patient had felt pain in the right lower abdomen immediately before the operation pain was also felt in the left lower abdomen No symptoms of thyrotoxicosis were noted

The operation revealed a normal-sized uterus The left ovary contained a tumour slightly bigger than an egg The right ovary was cystic When the tumour was dissected it was found to contain fairly soft cheesy tissue of malignant appearance



Fig. 4. Poorly differentiated thyroid tissue. Vein invaded by tumour tissue. Case 17. Haem. - van Gieson. × 70.

The microscopic examination of the specimen taken from the tumour showed tissue of varying structure and very varied type It was in part somewhat reminiscent of a granulosa cell tumour In these parts which were widely dispersed fairly small cells poor in plasma were seen to form more or less definite solid areas In other parts the tumour cells formed relatively clear long narrow strips which either lacked a distinct lumen or showed a small slit like lumen in the middle There were in addition better differentiated areas in which the tumour cells formed small follicles or narrow gland like ducts The malignant character of the tumour was evident from the fact that tumour tissue was visible in the lumen of some veins of the connective tissue capsule surrounding the tumour

On the basis of the above findings, the tumour was taken to represent a mixed form of granulosa cell and Sertoli cell tumour Dr Robert E. Scully (Massachusetts General Hospital Boston) to whom specimens of the tumour were sent and who kindly examined them however considered the tumour a malignant poorly differentiated struma ovarii (Fig 4)

Since the operation the patient has been treated with irradiation and seen regularly The last follow up examination was on February 20 1963 when the patient was well and no signs of recurrence were noted

Case 18

Married woman aged 72 No symptoms of thyrotoxicosis Pain in lower abdomen prior to operation

On operation a tumour approximately the size of a woman's fist was found in the left ovary The right ovary was normal When dissected the tumour was found to be cyst like and to consist partly of clear small cysts containing liquid

Histological diagnosis Ovarian teratoma (malignant struma ovarii) The microscopic specimen revealed that the tumour consisted partly of a wall composed of connective tissue alone the inner surface of which lacked epithelium and partly of areas of tissue which were definitely atypical in structure yet were recognizable as thyroid tissue There were both fairly well differentiated follicles and atypical epithelium infiltrating the connective tissue In one place there was a cystic cavity lined partly with columnar partly with squamous epithelium The tumour was a malignant teratoma in which thyroid tissue predominated

No information has been obtained on the patient's condition since the operation.

Case 19

Married woman aged 45 No information on parity or abortions No symptoms of thyrotoxicosis Slight pain in lower abdomen prior to operation and last menstruation 6 weeks pre-operatively

The right ovary showed a tumour diameter of 5 cm Both uterine tubes formed a hydrosalpinx, and there were fibroids in the uterus

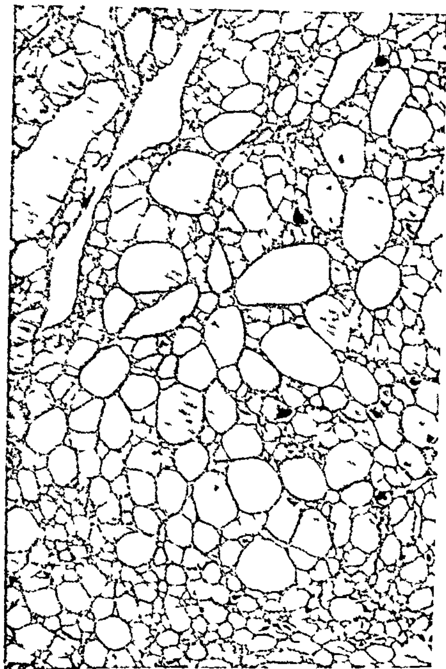


Fig 5 Well differential thyro d tiss e of collo d go tretype
Case 19 Haem - van G eson × 70

Histological diagnosis Dermoid cyst of the ovary Struma ovarii A microscopic specimen of the right ovary showed a dermoid cyst wall with an extensive area composed of thyroid tissue This was well differentiated primarily of struma colloides type The tumour tissue was adjacent to the hilus of the ovary on the other side of which a part of a corpus luteum in active phase was evident (Fig 5)

No information is available on the patient s condition since the operation

Review of the material

A total of 19 struma ovarii were examined by the laboratory of the I and II Clinics of Obstetrics and Gynæcology Helsinki University Central Hospital in 1951–1962 (Table II)

The youngest of the 19 patients with struma ovarii was 26 and the oldest 72 The mean age of the patients was 46 years Only 4 were under 40 According to Miller (1937) the mean age of patients with a dermoid ovarian cyst is 34 which is markedly lower than that of struma ovarii patients

Thirteen of the present series had the struma ovarii in the left ovary and 6 in the right ovary In all 19 cases the struma ovarii was unilateral Dermoid cysts are more frequently located in the right ovary and are comparatively often bilateral (Miller, 1937) A total of 5 patients showed pathological changes in the con tralateral ovary three had a dermoid cyst one had endometriosis and one had polycystic degeneration

The size of the struma ovarii *ranged from* that of *3 cm to* that of 20 cm

In 12 cases the patient had sought treatment for mechanical symptoms produced by the tumour, while in 7 cases the tumour represented a secondary finding One patient (Case 11) had distinct symptoms of thyrotoxicosis before the operation a large cervical goitre had been removed 7 years before the removal of struma ovarii No results of a laboratory examination are avail able in this case Four patients showed symptoms suggestive of thyrotoxicosis prior to operation though these cases had not been subjected to laboratory tests for this (Cases 1 2 8 and 9) For one patient (Case 6) the serum protein bound iodine was slightly increased (8 2 mg %) before the operation though no definite clinical symptoms of thyrotoxicosis were present. The serum

Table II *Detail presentation of the 19 cases of struma ovarii*

Case No	Age	Parity	Location and size of tumour	Histology	Malignant change	Contralateral ovary	Associated cervical goitre	Hyperthyroidism present	Symptoms
1	47	0	left, Diam 3 cm	Dermoid+struma ovarii	none	endometriosis	none	+—	asymptomatic
2	42	3	right, Diam 8 cm	Pure struma ovarii	none	normal	none	+—	pain in the back
3	29	3	right, Diam 10 cm	Dermoid+struma ovarii	none	dermoid	slightly enlarged	—	abdominal pain
4	48	0	left, Diam 12 cm	Dermoid+struma ovarii	none	normal	none	—	laryngopathy
5	43	1	left, Diam 3 cm	Pure struma ovarii	none	dermoid	none	—(SPI 8 3 mg %)	asymptomatic
6	61	0	left Diam 12 cm	Dermoid+struma ovarii	none	normal	none	—(SPI 8 2 mg %)	abdominal pain
7	46	0	left, Diam 12 cm	Dermoid+struma ovarii	none	normal	none	—	pain in the back
8	41	4	left Diam 5 cm	Pure struma ovarii	none	normal	none	+—	pain in the back and abdomen
9	58	4	left, Diam 20 cm	Dermoid+struma ovarii	none	normal	none	+—	abdominal pain
10	53	0	left, Diam 12 cm	Dermoid+struma ovarii	suspicious	normal	none	—	weight in lower abdomen
11	38	0	right Diam 12 cm	Dermoid+struma ovarii	none	normal	thyroidectomy	+	asymptomatic
1-	39	11	right, Diam 15 cm	Dermoid+struma ovarii	none	normal	none	—	asymptomatic
13	48	0	left, Diam 8 cm	Pure struma ovarii	none	removed for dermoid cyst	none	—	asymptomatic
14	46	4	left Diam 12 cm	Pure struma ovarii	none	normal	none	—	abdominal pain
15	-6	4	right Diam 12 cm	Pure struma ovarii	none	normal	none	—	abdominal pain
16	43	-	left, Diam 6 cm	Pure struma ovarii	none	normal	none	—	abdominal discomfort
	41	0	left Diam 8 cm	Struma maligna ovarii	yes	polycystic	none	—	abdominal pain
	7-	0	left, Diam 8 cm	Dermoid+struma maligna ovarii	yes	normal	none	—	abdominal pain
	45	0	right Diam 5 cm	Dermoid+struma ovarii	none	normal	none	—	asymptomatic

protein bound iodine of one patient (Case 5) was taken post-operatively and found to be sligtly increased (8 3 mg %) but the patient showed no symptoms of thyrotoxicosis One patient was found to have an enlarged thyroid gland without symptoms suggestive of thyrotoxicosis (Case 3)

One of the patients sought consultation because her voice had dropped in register Since her vocal chords showed no changes hormone analyses were made and they suggested a tumour excreting androgenic hormones (Case 4) A dermoid cyst containing much thyroid tissue was removed from the patient s left ovary Post operative hormone tests indicated normal values This patient showed no symptoms of thyrotoxicosis A report on the case has been published by Timonen Sonninen and Wichmann (1962) for its laryngopathic interest.

Of the patients of the series 9 patients were parous and 10 nulliparous

The thyroid tissue in struma ovarii as might be expected varies widely in structure not only from case to case but also in different parts of the same tumour Well differentiated tumour tissue differs little from the ordinary thyroid and goitre tissue Microscopic examination of Cases 7, 10, 11 and 13 showed more or less distinct changes in the epithelium and colloid, typical of endocrine activity Such changes were also noted by Castren (1941) in 2 cases The tumour tissue however shows more marked irregularity and structural variation than the thyroid tissue proper Less differentiated areas, identical or similar in structure to foetal adenomas of the thyroid are a relatively frequent finding Attempts to verify malignancy by morphological criteria encounter the same difficulties as in pathology of the thyroid and even more so because of the structural variations indicated above In a few exceptional cases anaplasia and pleomorphism may be so marked as to indicate immediately the malignancy of the tumour An infiltrating growth of the tumour tissue especially invasion of blood vessels is frequently the criterion on which the malignant character of a well differentiated tumour can be verified with certainty The microscopic specimens of two cases (Cases 17 and 18) revealed malignant growth

and of another (Case 10) suspected malignancy None of the patients of the series showed metastases

In 11 cases the thyroid tissue was found in a dermoid cyst, while the microscopic samples in 8 cases contained only thyroid tissue (pure struma ovarii) The present series included no cyst adenoma thyroid tissue

In a review of the series attention is attracted first by the high mean age of the patients and, second, by the fact that the struma ovarii, unlike the dermoid cyst, was more often located in the left than in the right ovary (The dermoid cysts containing struma ovarii were in 7 cases in the left, and in 4 cases in the right ovary) Another striking feature is that the series included no cystadenomas which, according to Smith, account for one third of all cases

Since the diagnosis of struma ovarii is usually made only on the basis of microscopical specimens, any possible symptoms of thy*rotoxicosis can only be evaluated afterwards This hampers* diagnosis of the case, especially if the symptoms of thyrotoxicosis are slight If thyrotoxicosis is diagnosed it should be verified that *it is not produced by the thyroid gland*

SUMMARY

Struma ovarii is a tumour occurring in the ovary and predominantly composed of thyroid tissue The thyroid tissue may be contained in a dermoid cyst (about half the number of cases), in cystadenoma (one-third of all cases), or the tumour may be composed of thyroid tissue alone (one-sixth of all cases) Struma ovarii provokes thyrotoxicosis in about 5-6 per cent of patients, while the incidence of malignant growth is about 5-10 per cent Metastases are found in about 5-6 per cent of cases, the metastases may be benign or malignant

In the present *series of 19 cases the thyroid tissue was located* in a dermoid cyst in 11 cases (about two-thirds of the cases) while in 8 cases (about one-third) the tumour was composed almost exclusively of thyroid tissue (pure struma ovarii) One patient only showed distinct symptoms of thyrotoxicosis 4 patients showed symptoms suggestive of thyrotoxicosis and another 2 patients had a slightly

increased serum protein bound iodine without clinical symptoms In 4 cases, changes in the thyroid tissue peculiar to endocrine activity were noticeable microscopically In 2 cases the thyroid tissue showed definite malignancy, and in another case suspected malignancy

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FEMALE GENITAL CARCINOMA AND THYROID DISEASE

BY

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It has long been known that patients with carcinoma of the corpus uteri not infrequently exhibit other pathologic conditions indicative of endocrine changes In recent years the possibility of a relationship between thyroid disturbances and carcinoma has received increasing attention The results of the present author s frequency analysis of a series of cases of cervical carcinoma in Sweden appear to support this view

Beatson (1896) reported satisfactory results in a small number of cases from combined treatment of carcinoma of the breast by mastectomy and bilateral oophorectomy together with administration of thyroid extract.

In 1934 Moratti (cit Dargent 1955) referred to an association between genital carcinoma and goitre and Stocks (1924) had pointed out earlier that goitre was observed remarkably often in patients with carcinoma of the digestive tract

Reding (cit Dargent 1955) found that diseases of the thyroid gland were three times more common among patients with carcinoma than with other diseases Loeser (1953 1954) noted that the risk of carcinoma was reltatively great among obese persons this he ascribed to hypofunction of the thyroid gland Rimbach (1954) reported that 16 (or 7 8 per cent) of 204 cases of corporeal carcinoma all of them over 50 years had previously

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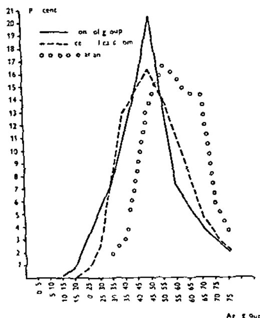


Fig 1 Age distribution for cervical and ovarian carcinoma and control group

between Scotland and England, the latter having the higher incidence of both goitre and carcinoma According to Spencer, goitre is rare in Iceland and the incidence of carcinoma is low compared with that in Denmark and Norway whence the population of Iceland largely originated In Japan too the figures are low for both goitre and carcinoma

The literature contains some significant data on mammary carcinoma and thyroid diseases In a series of 306 patients with mammary carcinoma Repert (1952) found a tenfold higher incidence of goitre than among noncancerous subjects (Table I)

Table I *Thyroid Disease in Females*

	Age Group	Per Cent
Expected with goitre	20–64	1 09–1 42
Breast cancer (306 cases)	18–75	12 0

Data from Metropolitan Life Insurance Co

undergone sub-total thyroidectomy In 5 of these 16 the thyroid treatment had been performed not more than 3 years before the carcinoma operation Out of a control group of 408 cases of benign gynæcological diseases only 3 had undergone thyroidectomy Rimbach considered that thyroidectomy leads to hypothyroidism, with diminshed cell respiration The impaired thyroid function results, moreover, in an increased secretion of thyrotropic and gonadotrophic hormones which, when the follicles are funtioning, results in hyperfolliculinæmia Rimbach pointed out that several authors had never seen hyperthyroidism and cancer together among their patients

Wijnbladh (1959) has stated that hypothyroidism would favour the development of carcinoma and stimulate growth of metastases He quotes similar findings by Crile, Starr and Goodwin (cit Wijnbladh, 1959)

Experimental studies on thyroid diseases and carcinoma have also been reported For instance in the mouse the destruction of the thyroid gland by means of radioiodine has been studied in relation to the increased tendency for tumours to develop (Furth, cit Loeser, 1954)

Windish (cit Rimbach, 1954) experimented with tissue cultures maintained in an atmosphere deficient in oxygen (see below)

Geographic data

Stocks (1924) refers to Bayards studies relating to the higher mortality from carcinoma in regions where goitre is endemic and reports his own investigation of the high incidence of carcinoma in such areas in Switzerland and Norway, and similar data from other countries

Bonafos and Gares (1952), from studies in North Africa, and Spencer (1954) on the basis or data from 15 countries, found that the incidence of carcinoma was high in areas where goitre was endemic As Spencer pointed out Holland has a higher carcinoma mortality than Belgium—in fact, among the highest in the world—and for centuries Holland has had a higher incidence of goitre than Belgium A similar relationship obtains

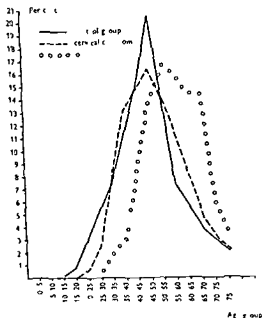


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	Age Group	Per Cent
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Breast cancer (306 cases)	18–75	12 0

Data from Metropolitan Life Insurance Co

In another series comprising 89 patients with mammary carcinoma Moehlig (1953) found goitre in 12, while sub-total thyroidectomy had been performed in 10 others

Loeser and Feldberg (1954) found the histamine content of skin to be lower in patients with carcinoma than in non cancerous subjects Accordingly, these authors considered that if patients with allergic disorders were found to have a lower frequency of carcinoma than other persons this might be due to a high level of histamine

In his account of 6 years experience of large doses of thyroid extract in inoperable cases of mammary and genital carcinoma Loeser expressed the view that the growth is retarded by this form of therapy In addition, over the same period he had used small doses of thyroid extract to prevent relapse after radical surgery for mammary and genital carcinoma The results encouraged him to experiment on a larger scale

Comparing an autopsy series of 207 patients with mammary carcinoma with a group of 248 subjects that had died from non cancerous diseases, Sommers (1955) found a disproportionally high number of cases with hyperplastic changes in the ovaries, suprarenal glands, pancreas and hypophysis, whereas the thyroid glands displayed *atrophic* changes that were not due to cachexia

Ellerker (1956) studied 2 series (i) A group of 100 women aged from 40 to 60 years, who had undergone thyroidectomy, mammary carcinoma was recorded in 6 per cent and cervical carcinoma in 1 per cent The mean age at the examination was 49 years and at thyroidectomy 42 years (ii) A group of 157 women with histologically confirmed mammary carcinoma were examined for goitre Twelve were found to have had thyroid diseases (7 6 per cent)

From an analysis of 617 cases of thyroid diseases and 13,261 cases of carcinoma, Desaive (1956) claimed to have found a connection between carcinoma and *thyroid disease* He reports instances where carcinoma had been preceded by goitre and patients who had undergone surgery for malignant tumours and where thyrotoxicosis or atoxic goitre had appeared subsequently He interpreted the thyroid manifestations as an anti cancer reaction of the body He also reported cases of concurrent car

cinoma and goitre, the latter of which he sees as the body s defence against carcinoma

Interesting studies on reduced thyroid function in patients with metastatic mammary carcinoma have been reported by Edelstyn et al (1958) Thyroid function was normal in subjects with locally restricted carcinoma of the breast Edelstyn et al noted an abnormally low thyroid function in patients that should undergo hypophysectomy for mammary carcinoma they displayed clear signs of hypothyroidism, which was confirmed by laboratory tests

Bayard (cit Rimbach 1954) considered that the normal cell derives some protection against malignant degeneration through the increased oxidation accompanying hyperthyroidism Conversely, hypothyroidism might be expected to restrict the cell respiration Bayard refers to Otto Warburgs (cit Rimbach 1954) studies on the metabolism of normal and carcinoma cells Warburg considers that there is an absolute deficiency of oxygen in carcinoma tissue rather than an inability of the carcinoma cells to oxidize lactic acid. According to Graffi, Windisch (cit Rimbach, 1954) succeeded some years ago in producing carcinoma in tissue cultures maintained under conditions of oxygen deficiency

Material

The term thyroid diseases or thyroid disorders as used in this paper covers atoxic and toxic goitre myxoedema and thyrotoxicosis without goitre of the latter two conditions there were only a few cases Thyrotoxicosis is used instead of Basedow s disease or exophthalmic goitre the term almost invariably used in the case records

In an analysis of some 10 000 cases of cervical carcinoma for the period 1946–1960 at the Jubilee Clinics in Stockholm (Radiumhemmet) Gothenburg and Lund and the Departments of Radiotherapy at Malmö and Uppsala data on thyroid diseases were noted The cases of cervical carcinoma from these departments constitute practically all known cases of this disease in Sweden for since 1928 radiotherapy has been the main form of

treatment for this condition, and the treatment has been centralized at these five hospitals

Also included in the investigation were patients who had undergone surgical treatment for apparently benign disease, but in which cervical carcinoma had been detected on histological examination In addition, cases were included in which, for various reasons, no treatment had been considered justified This group includes patients who were referred to the radiotherapy departments for possible treatment That these various groups together constituted practically all the cases of carcinoma of the cervix uteri in Sweden was confirmed by an examination of the carcinoma register for 1958

The data relating to thyroid disorders on the record sheets are occasionally sparse, especially in the cases referred for treatment but where for some reason none was performed The incidence of thyroid disorders for all the departments calculated from the records was 2 98 per cent

Since the control series for this investigation was obtained entirely from the region served by Radiumhemmet and the in

Table II *Analysis of Control Group According to Various Diseases and Associated Number of Cases of Thyroid Disorders (Radiumhemmet 1946–1960)*

	Myoma of Uterus	Postmenopausal Bleeding	Dysfunctional Uterine Haemorrhage	Benign Ovarian Tumour Ovarian Cyst	Diverse Gynec
Number of subjects	539	682	965	329	992
Cases of thyroid disease					
Number	21	32	32	13	23
Per cent	*3 90*	*4 69*	*3 32*	*3 95*	2 32

	Diverse Vaginal & Cervical	Endometriosis	Salpingitis Pelvicperitonitis (other than Tb) Pyometra	Tb Salpingitis & Endometritis	Affections of Vulva & Urethra	Non Gynaec Disorders	Total without Carcinoma	Total of Thyroid Disorders
Number of subjects	537	286	119	45	108	333	4935	
Number	10	4	3	—	—	7		145
Per cent	1 86	1 40	2 52			2 10	2 94	

cidence of thyroid disorders was found to be much the same at all the radiotherapy departments the comparisons were subsequently restricted to the cases of cervical carcinoma at Radiumhemmet These numbered 5819 (Table IV) and constituted about 60 per cent of those for the whole country for the period 1946–1960 By this means as valid a comparison as possible between the carcinoma and control series was ensured

To throw further light on the problem of a possible connection between thyroid disease and female genital carcinoma the record cards for ovarian carcinoma were taken from the Departments of Gynæcology at Linköping and Norrköping for 1946–1962 comprising 187 cases (Table IV) Cases of metastatic ovarian carcinoma were excluded from the series which comprised pure ovarian carcinoma and carcinomatously degenerated cystomas

Cases of ovarian carcinoma were collected from 2 hospitals out

Table III *Distribution of the Cervical and Ovarian Carcinoma Series and the Control Group According to Age*

Age Group (Yr)	Control Group No	Control Group Per Cent	Cervical Carcinoma No	Cervical Carcinoma Per Cent	Ovarian Carcinoma No	Ovarian Carcinoma Per Cent
0–5						
5–10						
10–15	3	0 06				
15–20	39	0 79	4	0 07		
20–25	147	2 98	40	0 69		
25–30	267	5 41	157	2 70	1	0 53
30–35	368	7 46	503	8 64	4	2 14
35–40	542	10 98	761	13 08	6	3 21
40–45	743	15 06	885	15 21	16	8 56
45–50	1007	20 41	939	16 14	26	13 90
50–55	709	14 37	835	14 35	31	16 58
55–60	363	7 36	631	10 84	30	16 04
60–65	292	5 92	476	8 18	27	14 44
65–70	196	3 97	286	4 91	27	14 44
70–75	153	3 10	183	3 14	12	6 42
75–	106	2 15	119	2 05	7	3 74
Total	4335	100 00	5819	100 00	187	100 00

Radiumhemmet 1946–1960
Linköping and Norrköping 1946–1962

Table IV *Survey the Results*

Age Group (Yrs)	Control Group	Thyroid Disorders No	Thyroid Disorders %	Cervical Carcinoma	Thyroid Disorders Observed	Thyroid Disorders Expected	Ovarian Carcinoma	Thyroid Disorders Observed	Thyroid Disorders Expected
0–5									
5–10									
10–15	3								
15–20	39			4					
20–25	147	1	0 68	40		0 27			
25–30	267	1	0 37	157		0 58	1		0 00
30–35	368	7	1 90	503		9 56	4		0 08
35–40	542	12	2 21	761		16 82	6		0 13
40–45	743	20	2 69	885		23 81	16		0 43
45–50	1007	27	2 68	939		25 17	26		0 70
50–55	709	28	3 95	835		32 98	31		1 22
55–60	363	17	4 68	631		29 53	30		1 40
60–65	292	17	5 82	476		27 70	27		1 57
65–70	196	4	2 04	286		5 83	27		0 55
70–75	153	9	5 88	183		10 76	12		0 71
75–	106	2	1 89	119		2 25	7		0 13
Total	4935	145	2 94	5819	190	185 26	187	21	6 92
Per cent					3 27			11 23	

side the radiotherapy departments with a view to obtaining as representative a series as possible of this disease The special clinics received for the most part only the cases for which the prognosis was fairly good, in contrast to cervical carcinoma, of which, as mentioned above, practically all stages occurred

Since there is no information on the incidence of thyroid diseases in Sweden nor, with accurate age distribution,—with some exception for breast carcinoma—in the foreign literature (Table I) (Repert, 1952), a noncancerous series was examined for thyroid disorders This comprised women who presented at the Department of Gynaecology, Radiumhemmet, during the period 1946–1960 with a number of diseases other than carcinoma—4 935 cases altogether (Table II) The diagnoses are given in Table II Where there was a history of any other form of carcinoma including skin carcinoma the patient was not included in the series The distribution of the cervical and ovarian carcinomas and the control group with respect to age is given in Table III

It is seen from Table III and Fig 1 that slightly younger age groups were represented in the control group than in the cervical carcinoma series This discrepancy is still more marked in the comparison with the ovarian carcinoma series, which is most strongly represented in two higher age groups To obtain comparable figures, therefore, account had to be taken of the occurrence of the thyroid diseases in the various age groups for the three series

The number of cases of thyroid disorders in each age group was calculated as a percentage of the control group (Table IV), and the frequencies so obtained were applied to the age groups of the two carcinoma series In each of the carcinoma series the expected number of thyroid disorders in the age groups were then added and the expected figures compared with the observed ones (Table IV) In this way a valid comparison could be made between the control and carcinoma series

Table II shows the distribution of thyroid disorders according to diagnosis in the control group

An attempt was made to obtain from the record cards an impression of the types of thyroid disorders (Table V)

Results

The observed number of thyroid diseases in the cervical carcinoma series was 190 The number expected on the basis of the frequency in the control series was 185 (Table IV)

In the ovarian carcinoma series, the observed number of thyroid disorders was 3 times as great as the expected number—21 and 6 9 respectively (Table IV)

A preliminary examination of the ovarian carcinoma series at the Department of Gynæcology South Stockholm Hospital showed the same trend as for the Linkoping and Norrkoping series

Discussion

It is open to question whether the selection of the control group was the best possible or whether a more representative comparison group could have been obtained There is ample

Table IV *Survey the Results*

Age Group (Yrs)	Control Group	Thyroid Disorders		Cervical Carcinoma	Thyroid Disorders		Ovarian Carcinoma	Thyroid Disorders	
		No	%		Observed	Expected		Observed	Expected
0–5									
5–10									
10–15	3								
15–20	39			4					
20–25	147	1	0 68	40		0 27			
25–30	267	1	0 37	157		0 58	1		0 00
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Per cent					3 27			11 23	

side the radiotherapy departments with a view to obtaining as representative a series as possible of this disease The special clinics received for the most part only the cases for which the prognosis was fairly good, in contrast to cervical carcinoma, of which, as mentioned above, practically all stages occurred

Since there is no information on the incidence of thyroid diseases in Sweden nor, with accurate age distribution,—with some exception for breast carcinoma—in the foreign literature (Table I) (Repert, 1952), a noncancerous series was examined for thyroid disorders This comprised women who presented at the Department of Gynæcology, Radiumhemmet, during the period 1946–1960 with a number of diseases other than carcinoma—4 935 cases altogether (Table II) The diagnoses are given in Table II Where there was a history of any other form of carcinoma including skin carcinoma the patient was not included in the series The distribution of the cervical and ovarian carcinomas and the control group with respect to age is given in Table III

It is seen from Table III and Fig 1 that slightly younger age groups were represented in the control group than in the cervical carcinoma series This discrepancy is still more marked in the comparison with the ovarian carcinoma series which is most strongly represented in two higher age groups To obtain comparable figures therefore, account had to be taken of the occurrence of the thyroid diseases in the various age groups for the three series

The number of cases of thyroid disorders in each age group was calculated as a percentage of the control group (Table IV), and the frequencies so obtained were applied to the age groups of the two carcinoma series In each of the carcinoma series the expected number of thyroid disorders in the age groups were then added and the expected figures compared with the observed ones (Table IV) In this way a valid comparison could be made between the control and carcinoma series

Table II shows the distribution of thyroid disorders according to diagnosis in the control group

An attempt was made to obtain from the record cards an impression of the types of thyroid disorders (Table V)

Results

The observed number of thyroid diseases in the cervical carcinoma series was 190 The number expected on the basis of the frequency in the control series was 185 (Table IV)

In the ovarian carcinoma series, the observed number of thyroid disorders was 3 times as great as the expected number—21 and 6 9 respectively (Table IV)

A preliminary examination of the ovarian carcinoma series at the Department of Gynæcology South Stockholm Hospital, showed the same trend as for the Linkoping and Norrkoping series

Discussion

It is open to question whether the selection of the control group was the best possible or whether a more representative comparison group could have been obtained There is ample

Table V *Thyroid Disorders in Cervical*[1] *and Ovarian*[2] *Carcinoma Series and in the Control Group,*[1] *Distribution According to Type of Disorder and Treatment*

	Op for Goitre		Op for Thyrotoxicosis		X Rays for Thyrotoxicosis		Radioiodine		Thiouracil for Thyrotoxicosis		Goitre and Others		Total
	No		No		No	%	No	%	No	%	No		
Cervical carcinoma	96	50 5	52	27 4	4	2 1	1	0 5	5	2 6	32	16 8	190
Control group	67	46 2	40	27 6	2	1 4	2	1 4	5	3 4	29	20 0	145
Ovarian carcinoma	5	23 8	12	57 1							4	19 0	21
Total	168		104		6		3		10		65		356

[1] Radiumhemmet, 1946–1960
[2] Linkoping and Norrkoping, 1946–1962

evidence that it would have been difficult from many aspects to obtain better As mentioned above, the control series was derived from the area served by Radiumhemmet and represented a large part of the Swedish population Moreover, the record sheets are made out in much the same way as for the carcinoma cases On the other hand, it is possible that myomas, post menopausal bleeding and benign ovarian tumours and cysts may have apparently increased the incidence of patients with thyroid disorders (Table II)

While it is true that the ovarian carcinoma series represents only one region of Sweden, the incidence of thyroid diseases is probably not different in Östergotland from that in the country as a whole Moreover, this series covers a period of 17 years and examination of the ovarian carcinoma cases at the Department of Gynæcology, South Stockholm Hospital, suggested an increase in the incidence of thyroid disorders over the same period

As Table V shows, 77 per cent of the cervical carcinoma series found to have thyroid disorders underwent operation, 27 per cent of them for thyrotoxicosis The corresponding figures for the ovarian carcinoma series were 81 and 57 per cent, the latter being a strikingly high proportion, for the control group the figures were 74 and 27 per cent respectively

The frequency of thyroid disorders was calculated for the

various diagnosis groups of the control series (Table II) Three groups had a higher frequency of thyroid disease than the 3 27 per cent for cervical carcinoma namely myoma of the uterus (3 90 per cent), post menopausal haemorrhage (4 69 per cent) and benign tumours and cysts of the ovaries (3 95 per cent) Owing to technical difficulties these figures were not corrected for age distribution The differences between the expected and the observed values are probably unimportant. If these three groups are excluded from the control series, the number of subjects is 3 385 and the frequency for the remaining groups 2 33 per cent The frequency of thyroid disorders for the cervical carcinoma group would then be considerably higher

It is difficult to judge whether the frequency of thyroid disorders was higher for the cervical carcinoma series than for the control series but on the available evidence, this is not improbable Be this as it may the frequency of thyroid disorders was three times as high in the ovarian carcinoma series as for the control group, even though they were overrepresented in the latter

It is natural to suppose that hypothyroidism would gradually develop as a consequence of thyroidectomy in atoxic goitre The same would probably apply to thyrotoxicosis, the treatment for which might result in a gradual development of a hypothyrotic condition

It is evident from the findings of this and similar studies that as a measure in the prevention of carcinoma more attention should be given to patients with thyroid diseases There is need for intensifying research on the role of thyroid hormones in carcinoma Persons undergoing operation for goitre should be checked regularly for the rest of their lives as regards both the actual thyroid function and the possibility of an association between thyroid disease and carcinoma

Conclusions

The apparently higher frequency of thyroid disorders in the series of cervical and ovarian carcinomas than in the control group supports the observations elsewhere in Europe and in the

United States relating to other forms of carcinoma such as corporeal and mammary carcinoma

The association is particularly marked with ovarian carcinoma, among which patients the frequency of thyroid disorders was three times as high as for the control group

SUMMARY

Reports from several countries suggest the possibility of an association between thyroid disorders and carcinoma However, in the reported investigations the respective materials were not grouped according to age In the present study the incidence of thyroid disorders in a cervical carcinoma series numbering some 10,000 cases and covering the period 1946–1960, the frequency of thyroid diseases was found to be 2 98 per cent

For a small group of 187 cases of ovarian carcinoma covering *the period 1946–1962 and analysed in the same respect,* the corresponding frequency was 11 23 per cent

About 60 per cent of the cervical carcinoma series, with a frequency of thyroid disease of 3 27 per cent, and the whole of the ovarian carcinoma series, were compared with a control group consisting of some 5,000 non-cancerous women grouped according to age

The findings of this study support the supposition of a connection between carcinoma and thyroid disease as regards both the ovarian and the cervical form, but in the latter case the association was less pronounced For the ovarian carcinoma series the frequency of thyroid disorders was about three times as high as for the control group

In the interest of preventing carcinoma a sharp look-out should be kept on patients with thyroid diseases, and research on the role of the thyroid hormones in carcinoma should be intensified Persons undergoing goitre operations should be checked regularly for the rest of their lives

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